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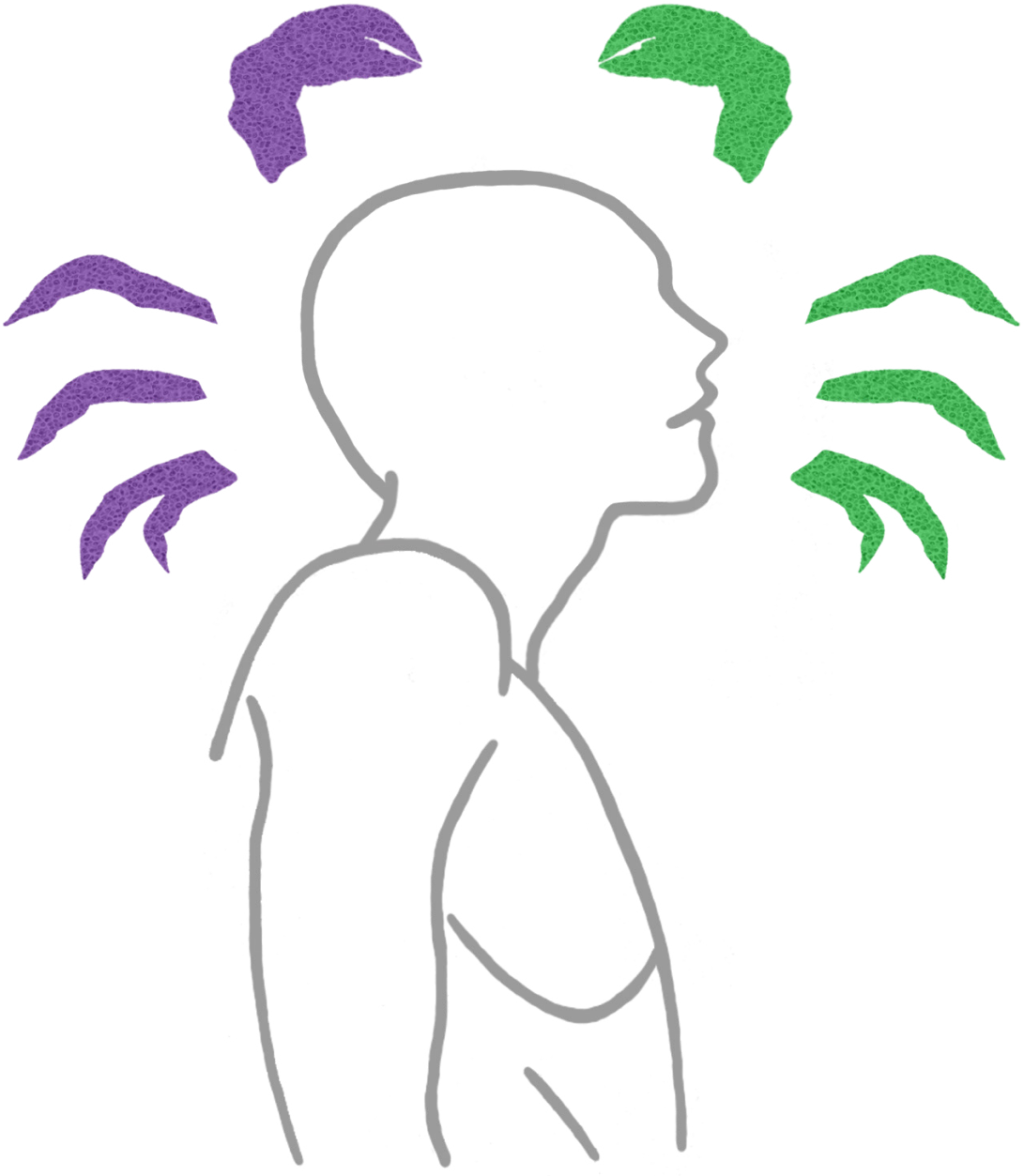

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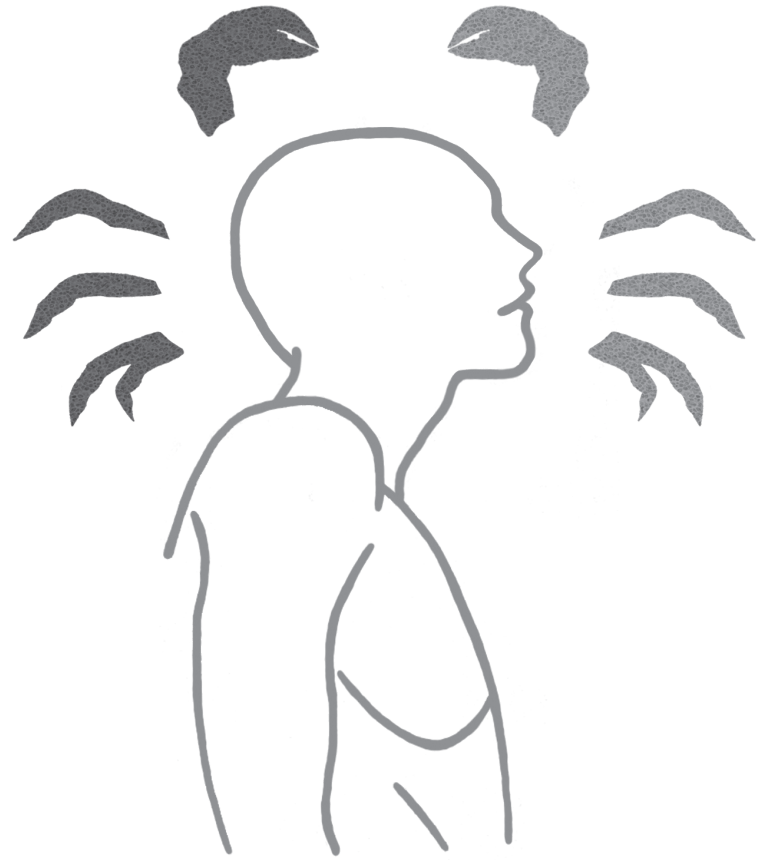
CHAPTER 1

General introduction



LYMPHOMAS: SUBTYPES, INCIDENCE, SURVIVAL AND PREVALENCE

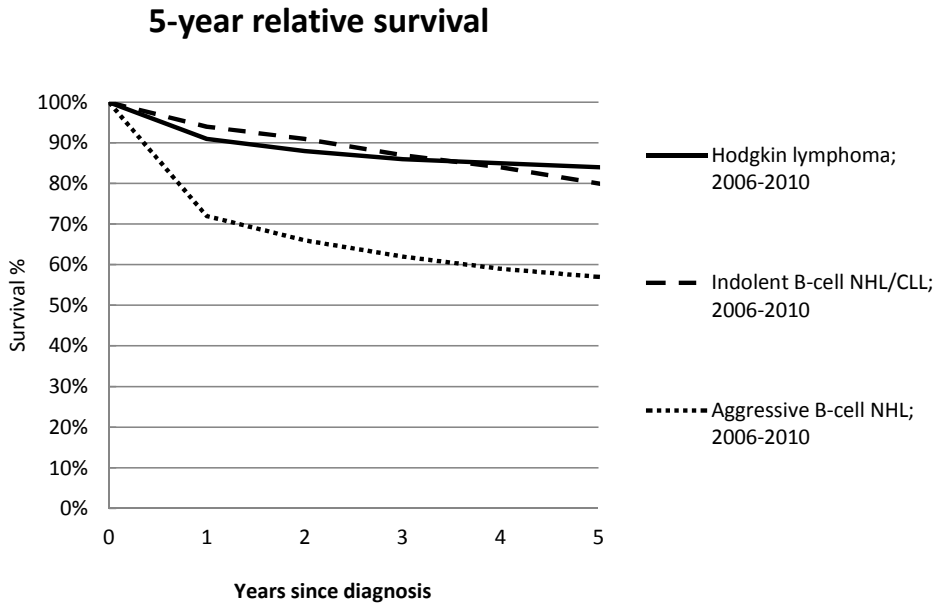
Lymphomas are defined by an abnormal proliferation of malignant B or T lymphocytes. Two major groups can be distinguished, i.e. Hodgkin Lymphoma (HL) and non-Hodgkin lymphomas (NHL). HL is named after Thomas Hodgkin, who first described abnormalities in the lymph system in 1832[1]. NHLs are a diverse group of more than fifty lymphomas that include any type except HL[2], whereby the most common types are diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). The latter types of lymphoma are categorized as indolent, incurable but with a good prognosis even without treatment, whereas the former are/or become aggressive, causing rapid deterioration and death if untreated[2, 3]. However, most patients with aggressive lymphomas respond well to treatment and are curable[2, 3]. The prognosis depends on the disease stage and the correct classification of the disease, which is established after examination of a biopsy by a pathologist.

Incidence and age of onset are quite different for HL and NHL. The annual incidence of HL is 1 in 37,000, with approximately 400 new diagnoses in the Netherlands[4], 5,600 in Europe[5] and 8,500 in the US[6]. Onset occurs most frequently between the ages of 20 and 35 years. With respect to NHL, the annual incidence is 1 in 5,000, with approximately 3,500 new diagnoses in the Netherlands[4], 58,000 in Europe[5] and 65,000 in the US[6]. The disease occurs predominantly in individuals aged over 45 years.

Advances in lymphoma treatment have led to longer survival, also in the south of the Netherlands[7-9]. To date, more than 80% of patients diagnosed with HL are expected to be disease-free at five years or more after diagnosis[4, 6]. The overall 5-year relative survival rate for patients with NHL (2003-2009) is 50-82%[6, 8]. The statistics vary, depending on the NHL type, stage of disease at diagnosis, treatment, and age of the patient. The 5-year relative survival of patients with HL, and indolent and aggressive NHL in the Netherlands (2006-2011) is displayed in Figure 1.

Additionally, the conditional 5-year relative survival, survival estimated for patients who have already survived a certain period of time, improves strongly for patients with aggressive NHL in the first year after diagnosis from 48% at diagnosis to 68% at 1 year after diagnosis. After the first year, the 5-year relative survival improves gradually to 93% after 16 years[10]. For indolent NHL, the conditional 5-year relative survival improves slightly with each additional year survived up to 91% after 16 years[10]. The increase in survival results in more patients who have or ever had lymphoma. A worldwide estimate shows around 1,021,400 men and women to be still alive in 2008, up to five years after their lymphoma diagnosis[11]. In the Netherlands, the twenty-year prevalence of HL, with 3,400 patients in the year 1990, is expected to increase to approximately 6,300 patients in 2020 and from 6,400 to approximately 32,000 patients with NHL (Figure 2)[4]. Instead of the term ‘cancer patients’, ‘cancer survivors’ is increasingly being used, especially in the US. The definition of cancer survivors include all living persons who ever received a diagnosis of cancer[12] and is often used by researchers and cancer patient organizations. However, clinicians in the Netherlands prefer to use cancer patients, especially among patients with lymphomas

Figure 1. Five-year relative survival for patients with Hodgkin and indolent and aggressive non-Hodgkin lymphoma in the Netherlands (2006-2010).



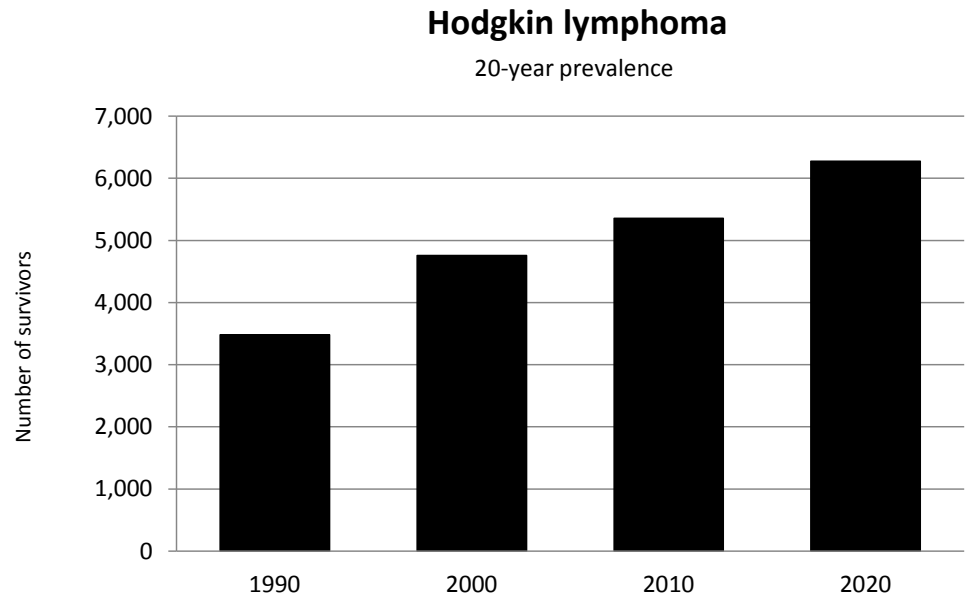
Note. Source: Netherlands Cancer Registry

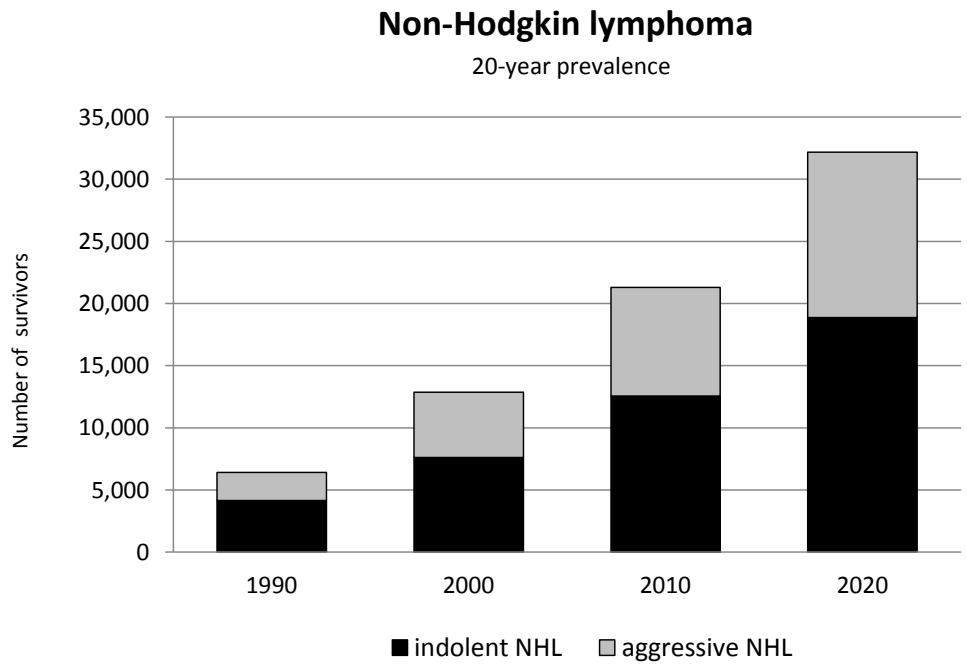
that cannot be cured. Therefore, both the terms cancer patients and cancer survivors are being used interchangeably in this thesis.

HEALTH-RELATED QUALITY OF LIFE AND PATIENT REPORTED OUTCOMES

Since cancer patients survive longer, health-related quality of life (HRQoL) and other patient reported outcomes (PROs) are more and more recognized to be important[13, 14]. Particularly because many survivors continue to face physical and psychosocial problems after completion of primary treatment[15]. HRQoL is a multidimensional construct that covers patients' perceptions of his or her physical, emotional, social and cognitive functions and disease and/or treatment related symptoms and represents patients' subjective experience with cancer. In the past decade a growing number of studies have documented the high prevalence of short-term effects (e.g. hair loss, pain, nausea and vomiting, anemia), long-term effects (e.g. fatigue, pain, memory problems and sexual dysfunction) and late effects (e.g. second malignancies, cardiovascular disease and osteoporosis) of cancer treatment[12, 16-18]. Research also shows that many survivors experience a deteriorated HRQoL, fear of recurrence, high levels of anxiety and depression, employment, insurance and financial problems and relationship difficulties[12, 19]. This knowledge has been primarily gained from survivorship studies that focused on survivors of common types of solid tumors like, breast, colorectal and prostate cancer[20].

Figure 2. Twenty-year prevalence of Hodgkin and non-Hodgkin lymphoma in the Netherlands on 1990, 2000, 2010 and the prognosis for 2020.





Note. Source: Netherlands Cancer Registry

RATIONALE FOR THIS THESIS

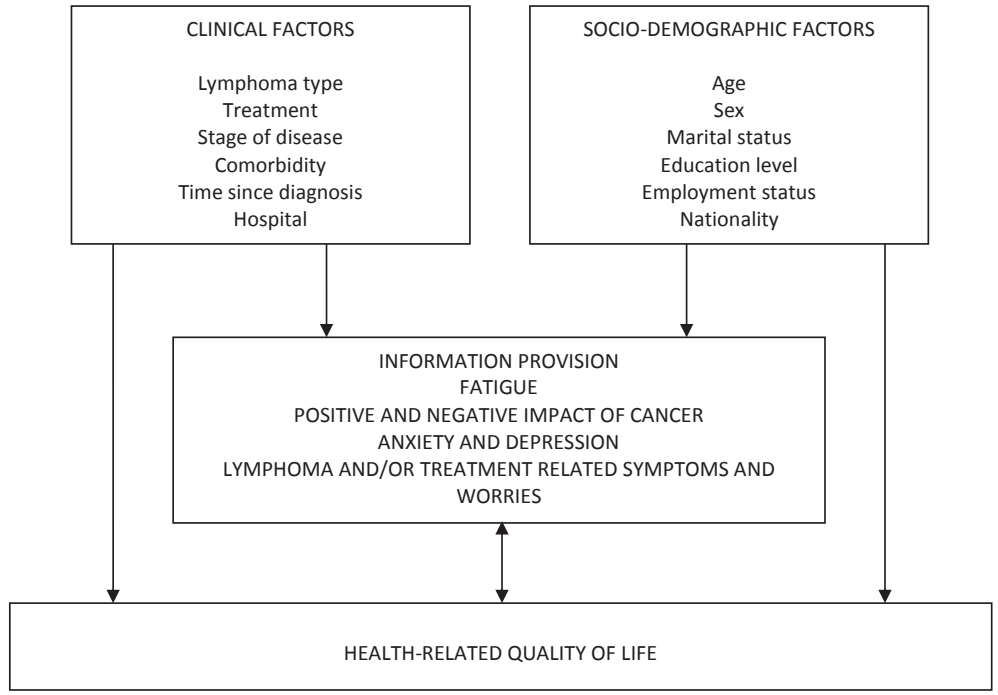
Up to now, the number of studies focusing on (long-term) HRQoL and disease and treatment-related symptoms of patients with lymphoma is limited. Since increasing numbers of lymphoma patients undergo (ever) changing treatment regimens, a careful evaluation of survival improvements, as well as potential side effects of treatment, and (long-term) HRQoL is required. Besides evaluating these effects of (targeted) therapies in RCTs, population-based observational studies are needed to study the effects of these therapies in patients treated in daily practice including elderly and patients with comorbid diseases. Studying long-term effects of different treatments provides information on the medical and psychosocial needs of patients and its determinants. This information will help to evaluate the functional effectiveness of the treatment and help clinicians to inform cancer patients and survivors about the potential late effects from the specific treatment they receive(d). It can also give direction to the recognition of problems and surveillance of those survivors who are at high risk for late consequences of cancer treatment.

Most studies among lymphoma survivors that have been performed up to now focused on biological endpoints such as second malignancies and cardiovascular disease, predominantly among Hodgkin lymphoma survivors[17, 18, 21-24]. The studies that did focus on the HRQoL of lymphoma patients commonly had a cross-sectional design, studied HRQoL as part of a randomized clinical trial or studied HRQoL among NHL patients in general[25-48]. Although these studies provide a good overview of the HRQoL of patients at a certain point in time, the course of HRQoL and the persistence of symptoms over time remains unknown, elderly patients and patients with comorbidities are underrepresented, or the HRQoL of different types of NHL is not examined. Studies focusing on populations including elderly and patients with comorbid conditions are of critical importance as comorbidity and age probably affect the HRQoL of patients and thus influences treatment decision making[49-51]. Furthermore, HRQoL studies among different types of NHL are important as prognosis, treatment modalities, and age of onset differ.

AIMS AND HYPOTHESES

Studies have shown that treatment and cancer itself can impact on the HRQoL of patients with solid tumors. Based on this knowledge, I developed a conceptual model with the perceived associations between clinical factors (such as treatment and lymphoma type) and socio-demographic factors (such as age, educational level and nationality) with HRQoL (Figure 3). It is expected that active treatments such as chemo- and immunotherapy impact more on the HRQoL of patients compared to patients following a watchful waiting approach. Furthermore, it was hypothesized that several other clinical and socio-demographic factors may impact on the HRQoL of patients and that patients reporting disease and or treatment related symptoms or anxiety and depressive symptoms may experience a worse HRQoL.

Figure 3. Conceptual model: associations between patient, tumor, treatment and hospital factors with patient reported outcomes.



In **Chapter 2**, the scientific literature regarding the impact of clinical (including treatment) and socio-demographic characteristics on HRQoL of HL and NHL patients was reviewed. Also the methodological strengths and limitations of the included studies were examined in this chapter. It appeared that mainly the evaluation of HRQoL following treatment among patients with subtypes of NHL was lacking. Therefore, the impact of targeted therapies on the HRQoL of patients for major types of NHL, i.e. DLBCL, FL and CLL/SLL, were studied in **Chapter 3, 4 and 5** respectively. In these chapters, we investigated if patients who received immunochemotherapy with more short-term toxicities would report a lower HRQoL compared to patients treated with treatments with less short-term toxicities or patients under active surveillance. We furthermore compared the HRQoL scores of patients with those of an age- and sex-matched normative population to investigate the impact of cancer and its treatment beyond the natural aging process and the impact of comorbidities.

Besides studying the impact of treatment and lymphoma itself on the HRQoL of patients I also evaluated the relation between disease and/or treatment related symptoms and anxiety and depressive symptoms and HRQoL (Figure 3). As many cancer patients with solid tumors report anxiety, depressive symptoms, and fatigue, I wanted to investigate the prevalence and

longitudinal course of anxiety and depressive symptoms among HL and DLBCL patients (**Chapter 6**) and the prevalence of persistent fatigue among NHL, both DLBCL and FL patients (**Chapter 7**).

Furthermore, patient information has proved to be an essential component of cancer care and rehabilitation[52] and providing adequate information to cancer patients can reduce the psychological burden and improve patients HRQoL and their satisfaction with care[53, 54]. We therefore investigated the level of perceived information provision and satisfaction with this information among patients with lymphoma or multiple myeloma in **Chapter 8**.
Cultural differences may affect the perception of the impact of cancer on HRQoL[55, 56] and attitudes towards health practice and illness may also be defined by culture[57]. To better understand the commonality of psychosocial problems between cultures, it is important to examine cross-national differences[58]. Therefore, we performed a cross-national study between Dutch and American (from North Carolina) NHL patients with respect to the positive and negative changes following cancer in **Chapter 9**.
At last, the main findings of this thesis will be discussed and implications for future research and clinical practice will be outlined in **Chapter 10**.

METHODS: POPULATION-BASED REGISTRIES

To perform these studies, a longitudinal population-based survey among HL and NHL survivors registered with the Eindhoven Cancer Registry (ECR) was set up. Data collection regarding HRQoL and other patient reported outcomes was done in PROFILES and detailed treatment data was obtained from PHAROS. All studies were conducted at the Comprehensive Cancer Center South (IKZ), the program owner of the ECR, which is part of Comprehensive Cancer Center the Netherlands (IKNL) since January 1st 2014.

Eindhoven Cancer Registry

The Eindhoven cancer registry (ECR) started in 1955, whereby data on all new cancer patients are collected directly form pathology reports and medical records. Since 1989, the population-based ECR is part of a program for nationwide cancer registration (Netherlands Cancer registry) and now hosts 2.4 million inhabitants, being referred to 10 general hospitals at 16 locations and is served by 6 regional pathology laboratories, 2 large radiotherapy institutes, and 1 neurosurgical center (Figure 4). The clinical data available from the ECR included date of diagnosis, tumor grade, histology, Ann Arbor stage[59], primary treatment, and patients background characteristics, including gender, date of birth, comorbidity and postcode.

PROFILES

PROFILES (Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship) is a registry for the study of the physical and psychosocial impact of cancer and its treatment from a dynamic, growing population-based cohort of both short and long-term cancer survivors[15]. PROFILES is a tool that enables data collection management; from inviting patients to participation in studies, to collecting patient-reported outcome data via web-based or mailed questionnaires and linking these data to clinical data from the ECR.

Figure 4. The current area of the Eindhoven Cancer Registry of the Comprehensive Cancer Centre Netherlands.

Normative population

HRQoL and other patient reported outcome data were also collected from a normative population of 2,040 individuals from the general Dutch population (CentER panel). This cohort is considered representative for the Dutch-speaking population in the Netherlands[60]. Based upon this normative population age- and sex-matched selections were made for the specific lymphoma samples. Comparison with an age- and sex-matched normative population provides information about the impact of cancer beyond the natural aging process and the impact of comorbidities.

PHAROS

PHAROS (Population-based Haematological Registry for Observational Studies) aims to contribute to the study of the effectiveness of targeted therapies for patients with hematological malignancies in a population-based setting[61]. Part of the effectiveness is the impact of these therapies on side effects and HRQoL among lymphoma patients. PHAROS is an extension of the Netherlands Cancer Registry and a collaboration between HOVON (Dutch Cooperative Group on Hemato-Oncology) iMTA (institute for Medical Technology Assessment) and IKNL. The PROFILES and ECR-data of patients on primary treatments were replenished with details on treatment from PHAROS.

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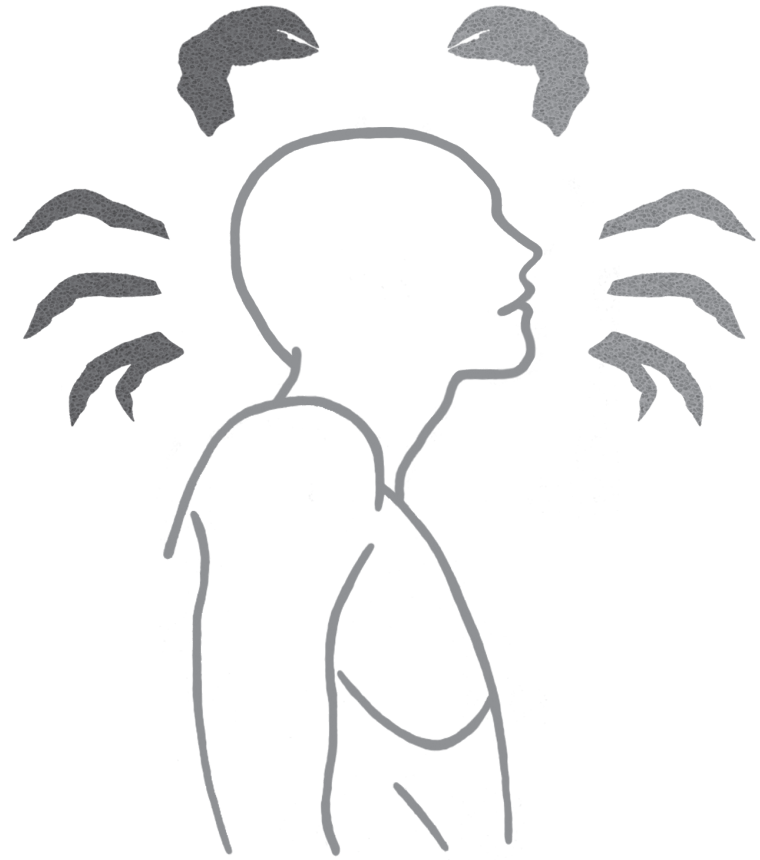
CHAPTER 2

The impact of treatment, socio-demographic and clinical characteristics on health-related quality of life among Hodgkin's and non-Hodgkin's lymphoma survivors: A systematic review



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ABSTRACT

Cancer survivors are at risk of experiencing adverse physical and psychosocial effects of their cancer and its treatment. Both Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL) survivors face problems that can affect their health-related quality of life (HRQoL). The authors systematically reviewed the literature on HRQoL among HL and NHL survivors. A PubMed and PsychINFO literature search for original articles published until May 2011 was performed. Twenty-four articles, which met the predefined inclusion criteria, were subjected to a quality checklist. HL survivors showed the most problems in (role) physical, social and cognitive functioning, general health, fatigue and financial problems. In addition, HL survivors treated with a combination of therapies, with older age and female sex reported worse HRQoL. NHL survivors showed the most problems in physical functioning, appetite loss, vitality and financial problems. Having had chemotherapy was negatively associated with HRQoL but no differences in chemotherapy regimens were found. Furthermore, in NHL survivors not meeting public exercise guidelines HRQoL is low, but can be improved with more exercise. More research on the longitudinal comparison between HL and NHL survivors and healthy controls should be performed in order to better understand the long-term (side) effects of treatment on HRQoL and possibilities to alleviate these.

INTRODUCTION

Treatment of cancer has improved considerably in the past decades resulting in more (long-term) survivors. A person diagnosed with cancer is defined a survivor from the moment of diagnosis through the balance of his or her life[1]. The number of cancer survivors in the United States (US) has increased steadily and is currently estimated to be 11.1 million[2]. The number of lymphoma survivors has relatively increased even more. On January 1, 2008, there were approximately 167,000 Hodgkin's lymphoma (HL) survivors, and approximately 454,000 non-Hodgkin's lymphomas (NHL) survivors in the US[2]. In the Nordic European Countries (NEC: Denmark, Faroe Islands, Finland, Iceland, Norway, Sweden), there were approximately 10,500 HL survivors, and approximately 31,500 NHL survivors at the end of 2007[3].

Although there are similarities between these subtypes of lymphoma, the incidence and age of onset are quite different. The annual incidence of HL is 1 in 35,000 in the US[2] and 1 in 47,000 in the NEC[3], with approximately 8,500 new cases in the US[2] and 558 new cases in the NEC[3] annually. Onset occurs most frequently between the ages of 20 and 35 years. Between 35 and 50 years it occurs less often, especially in females, but from the age of 50 onward there is again a rise in incidence with age[2]. The lifetime prevalence of HL is one in 430[2]. With respect to NHL, the annual incidence is one in 5,000, with approximately 65,000 new cases in the US[2] and 73,000 new cases in the European Union (NEC numbers are unavailable)[4]. The disease occurs predominantly in individuals aged over 45 years and the lifetime prevalence of NHL is one in 50[2].

Due to chemotherapy, radiotherapy, and stem cell transplantation, the survival of these patients has improved dramatically in the seventies and eighties, but has nowadays levelled off. In effect, most trials focus on maintaining the high level of cure, while reducing the long-term effects of treatment. To date, more than 80% of patients diagnosed with HL are expected to live free of disease for five years or more after diagnosis[5]. The overall 5-year survival rate for all types of NHL (1999-2005) is 50-60%. The statistics vary, depending on the cell type, stage of disease at diagnosis, treatment, and age of the patient[5].

As cancer survivors are living longer, they are at risk of experiencing adverse physical and psychosocial long-term effects of the fact they had cancer or of their treatment[6-9]. Especially the long-term HL and NHL survivors face specific problems, concerning mainly chronic medical as well as psychosocial complications that can affect their health-related quality of life (HRQoL). Fatigue, depression, marital disruption, and problems with infertility are frequently reported concerns by these survivors, not to mention problems with insurances and mortgages[6, 8-11].

Only recently, the focus of published papers has shifted from improvement of survival to HRQoL. In December 2009, a review concerning HRQoL in lymphoma survivors has been published[12]. This review described the HRQoL of both HL and NHL survivors combined, which may delude conclusions as differences in age of onset, treatment and overall survival time between HL and NHL greatly influences HRQoL. In addition, four prospective and two cross-sectional studies,

all published between 2004 and 2009, were not included in this review and especially these prospective studies contain important information. Furthermore, and most important, the review did not provide information about the clinical implications of its findings. Many studies base their conclusions on statistical significance, but clinical significance should also be studied for the representation of clinically important differences to patients. Our review will therefore distinguish itself by a separate discussion of both types of lymphoma, a more complete and update overview of studies, and by providing information about clinical significance of the findings. The aim of this systematic review was (1) to evaluate the quality of the included studies, (2) to identify the HRQoL domains and symptoms that are clinically relevant affected in HL and NHL survivors, (3) to evaluate the relation between treatment and HRQoL and (4) to evaluate potential differences in socio-demographic and clinical characteristics.

METHODS

Search strategy

The electronic databases of Pubmed and PsychINFO were searched to find all articles up to December 2010 using the terms 'Hodgkin's and 'non-Hodgkin's lymphoma' in combination with: survivors, long-term, (health-related) quality of life, and HRQoL. The reference lists of all publications were checked to retrieve additional publications.

Selection criteria

Studies in English on HRQoL in HL and NHL adult survivors were included if they used a multidimensional HRQoL questionnaire. Studies that merely focused on one-dimensional aspects of HRQoL such as fatigue, anxiety, or depression were excluded from this review, because this is not consistent with the multidimensional concept of HRQoL (i.e. the existential influence of disease on physical, emotional, and social functioning). Also, studies that involved a variety of tumours including HL or NHL, focused on adult survivors of childhood cancer, and studies not published in peer-reviewed journals were excluded. Furthermore, the focus of the study had to be either one or more of the following; (1) comparison with a normative population, (2) studying the relation between treatment and HRQoL, (3) studying the relation between socio-demographic or clinical characteristics and HRQoL. The search resulted in 270 hits. Based on titles and abstracts, 24 articles met our selection criteria and were included in this review (Figure 1).

Quality assessment

The methodological quality of the selected studies was assessed using a 12-item standardized checklist of predefined criteria which was a modified version of an established criteria list for systematic reviews (Table 1)[13, 14]. Each item of a study, which met our criteria, was assigned one point. If an item did not meet our criteria, was described insufficiently, or not at all, then zero points were assigned. The highest possible score was 12. Studies scoring ≥8 points were considered to be of 'high quality'. Studies scoring <6 points or 6-8 points were rated respectively as low and moderate quality.

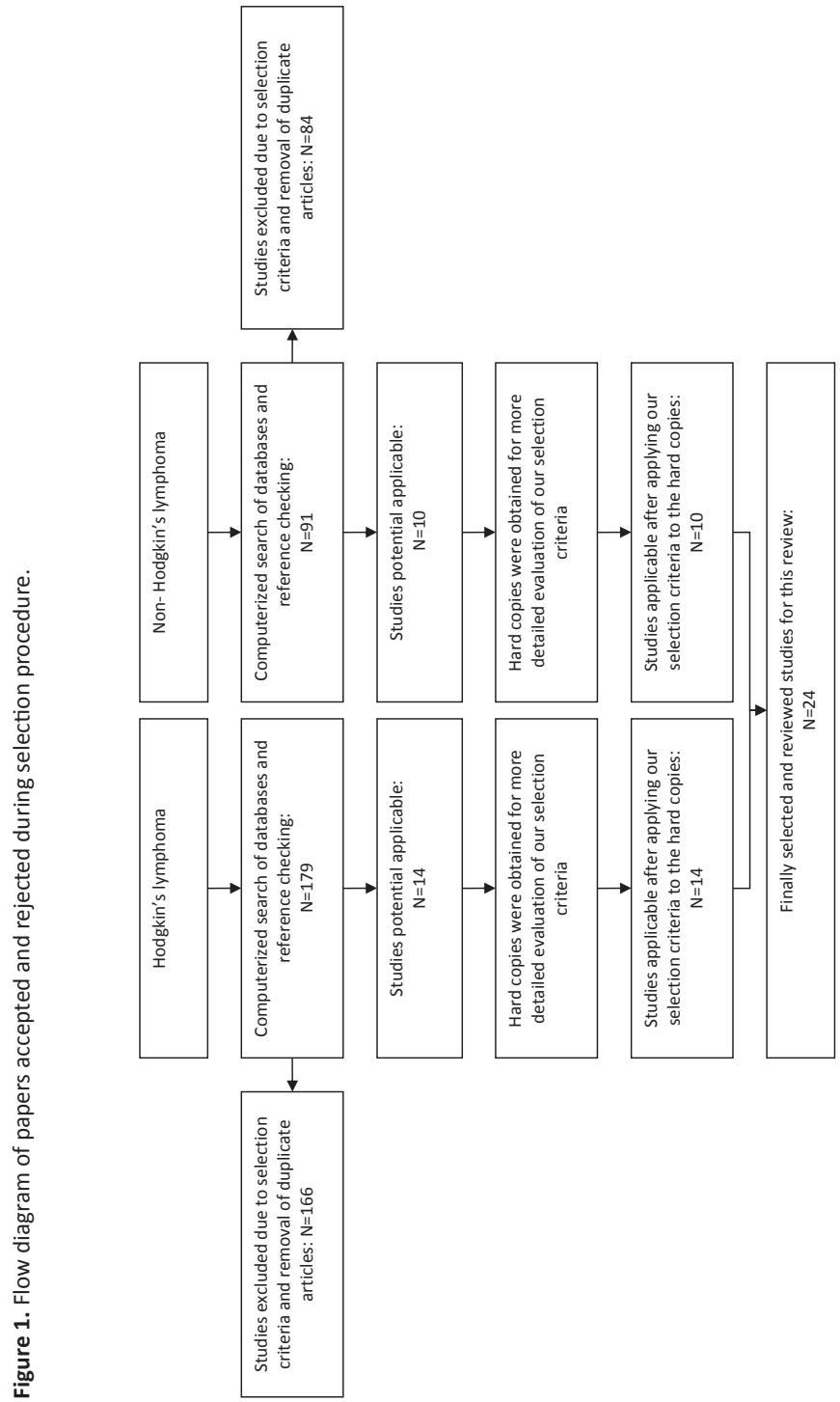

Figure 1. Flow diagram of papers accepted and rejected during selection procedure.

Table 1. List of criteria for assessing the methodological quality of studies on health-related quality of life among Hodgkin's and non-Hodgkin's lymphoma.

Positive if with respect to:
Quality of life assessment
1. A validated (Health-related) Quality of Life questionnaire is used (e.g. SF36, EORTC-C30).
Study population
2. A description is included of at least two socio-demographic variables.
3. A description is present of at least two clinical variables of the described patient population (e.g. tumour stage at diagnosis).
4. Inclusion and/or exclusion criteria are described.
5. Participation rates for patient groups are described and are more than 60%.
6. Information is given about the degree of selection of sample (information is given about the ratio respondents versus non-respondents).
Study design
7. The study size is consisting of at least 50 participants (arbitrarily chosen).
8. The data is prospectively gathered.
9. The process of data collection is described (e.g. interview or self-report).
Results
10. The results are compared between two groups or more (e.g., healthy population, groups with different treatment or age) and/or results are compared with at least two time points (e.g., longitudinally versus post-treatment).
11. Mean, median, standard deviations or percentages are reported for the most important outcome measures.
12. Statistical proof for the findings is reported.

Criteria for clinically important difference

The following criteria were used to determine clinically important differences. For the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), a score of ≥10 points difference on subscales reflects a clinical important difference [9, 15-18]. Concerning the SF-36, differences of ≥2 points for role physical functioning; ≥3 points for physical functioning, social functioning, bodily pain, general health, vitality, mental health and the component scales; ≥4 points for role emotional functioning are considered clinically meaningful[19, 20]. For the other questionnaires and some subscales Norman's 'rule of thumb' was used whereby a ≈ 0.5 SD difference indicates a threshold of discriminating change in HRQoL scores of a chronic illness[21].

RESULTS

Study characteristics

In total, 24 studies were included (14 HL[9, 15, 16, 22-32] and 10 NHL[11, 17, 33-40]) all published between February 1994 and November 2010. Only one study was conducted outside the US and Europe[40]. Time since diagnosis ranged between circa two months and 44 years. The most frequently used questionnaires of HRQoL were the EORTC QLQ-C30 (10 studies)[41] and the RAND Short Form-36

(SF-36) (11 studies)[42]. Two studies used the Schedule for the Evaluation of Individual Quality of Life–Direct Weighting (SEIQoL-DW)[43] and three studies used the Functional Assessment of Cancer Therapy-General (FACT-G)[44].

With respect to HL, two studies had a prospective design and twelve studies had a cross-sectional design. Of the 14 studies, ten cross-sectional studies compared HL survivors and the general population, two prospective and eight cross-sectional studies evaluated the relation with treatment, and two prospective and nine cross-sectional studies reported about potential differences in socio-demographic and clinical characteristics (Table 2). With respect to NHL, four studies had a prospective design and six studies had a cross-sectional design. Of the ten studies, two prospective and three cross-sectional studies compared NHL survivors and the general population, three prospective and two cross-sectional studies evaluated the relation with treatment, and nine studies reported about the potential differences in socio-demographic and clinical characteristics (Table 3).

The evaluation of the methodological quality of the studies by the reviewers (SO, FM, LP) yielded the following results. On items 1, 5, 7, 8, 9, 11, and 12 there was disagreement once, and on items 2, 3, and 10 there was no disagreement. On items 4 and 6 (see Table 1), there was disagreement a couple of times, mostly due to differences in interpretation of the text. These were solved through discussion in a consensus meeting. The methodological quality of all included studies ranged from 8 to 12 points and was thus considered to be of high quality. General shortcomings concerned mainly the lack of information on non-respondents (n=11) and the lack of a prospective design (n=16).

Hodgkin's lymphoma

HRQoL domains: HL survivors vs. normative samples

Four cross-sectional studies found clinically important lower physical functioning scores for survivors compared to a normative population[9, 26, 30, 32]. No clinically important differences were found in six studies[15, 22, 24, 27, 28, 31].

Five studies found that HL survivors had clinically important lower scores on social functioning compared to normative samples[9, 15, 22, 24, 26]. Three studies found no clinically important differences on social functioning[27, 28, 30].

One study among 98 survivors that survived more than 8 years found that HL survivors had clinically important lower scores on emotional functioning compared to the normative sample [22] while seven studies found no clinically important differences[9, 15, 24, 26-28, 30].

Five studies found that HL survivors had clinically important lower scores on role physical functioning compared to the normative sample[9, 22, 26, 27, 30]. Three studies found no clinically important differences[15, 24, 28].

No clinically important differences were found between HL survivors and normative samples with respect to Global health state (6 studies)[15, 22, 24, 27, 28, 31].

Three cross-sectional studies found that HL survivors had clinically important lower scores on general health compared to the normative sample[9, 26, 30] Two cross-sectional studies found no clinically important differences on general health[28, 31].

No clinically important differences were found between HL survivors and normative samples regarding mental health scores (4 studies)[9, 26, 28, 30].

Table 2. Overview of studies on HRQoL among Hodgkin's lymphoma survivors.

Study, year, country	N	Mean age, SD or range	Treatment	Time since diagnosis	Design	Quality of life instruments	Comparison norm population	Evaluation treatment effect	Evaluation other characteristics	General conclusions	Quality score*
Brandt et al. 2010. Germany[22]	98	Mean: not reported Range: 21-72	Conventional chemotherapy versus high dose chemotherapy and stem cell transplantation	1-24 years	Cross-sectional	EORTC-QLQ-C30	Yes, comparison health population	Yes	No	HL survivors have a reduced HRQoL compared to the healthy population. HL survivors who were treated with conventional chemotherapy had clinically important less dyspnoea complaints compared to survivors treated with high dose chemotherapy.	10
Loge et al. 1999. Norway[9]	459	Mean: 44 SD: 11.8	Chemotherapy, radiotherapy, or combined therapy	Mean= 12.2 years (3-23)	Cross-sectional	SF-36[1]	Yes, comparison with general population norms	Yes	Yes	HL survivors had lower scores than the normal controls on general health, physical functioning, role limitations, social functioning and vitality after adjustment for age, gender and educational levels. Long-term HL survivors have poorer HRQoL primarily in physical health. No differences between treatments were found.	10
Ganz et al. 2003. USA[23]	247	Mean: 33 Range: 17-85	Radiotherapy versus chemotherapy followed by radiotherapy	Mean=6 months, 1 year, 2 years	Prospective	SF-36	No	Yes	Yes	Patients with early stage HL experience a short-term (6 months) decrease in HRQoL and an increase in symptoms and fatigue with treatment. However, after 1 year these scores returned to baseline scores.	10
Gil-Fernandez et al. 2003. Spain[24]	46	Mean: 43 Range: 15-80	Chemotherapy, radiotherapy, or combined therapy	Mean= 7.6 years (0.8-22.1)	Cross-sectional	EORTC-QLQ-C30[2]	Yes, compared to healthy individuals of the faculty of medicine	Yes	Yes	Statistically significant differences were observed between HL survivors and controls in two functional scales. Physical function was significantly lower in patients than in controls and the social operation scale that refers to the social familial relationships of the individuals was also lower in patients than in controls. HL survivors also scored worse on the dyspnoea scale and reported more economical difficulties. No difference between treatments was found.	10

Table 2. Overview of studies on HRQoL among Hodgkin's lymphoma survivors. (Continued)

Study, year, country	N	Mean age, SD or range	Treatment	Time since diagnosis	Design	Quality of life instruments	Comparison norm population	Evaluation treatment effect	Evaluation other characteristics	General conclusions	Quality score*
Goodman et al. 2008. USA[15]	60	Mean: 43 Range: 24-65	Chemotherapy and autologous stem-cell rescue	Mean= 12 (6-18) years	Cross-sectional	EORTC-QLQ-C30	Yes, comparison with the general population	No	Yes	Global HRQoL of HL survivors was comparable with the general population, but for specific domains, respondents' scores indicated reduced functioning and worse symptoms: cognitive and social functioning, fatigue, insomnia and financial problems.	8
Greil et al. 1999. Austria[25]	126	Mean: 37 SD: 16.3 Range: 6-89	Chemotherapy, radiotherapy, or combined therapy	Mean= 10.5 years (0.9-34)	Cross-sectional	EORTC-QLQ-C30	No	Yes	Yes	The scores indicate high scores on HRQoL parameters in all subscales in HL survivors after a mean period of 9.1 years from the time of the initial diagnosis. HL survivors treated with combined modality therapy showed worse physical functioning and more fatigue, pain and dyspnoea.	10
Heutte et al. 2009. France[16]	935	Mean: not reported Range: 15-70	Chemotherapy, radiotherapy, or combined therapy	Mean=90 months (52-118)	Prospective, longitudinal	EORTC-QLQ-C30	No	Yes	Yes	HL survivors showed a significant improvement in most HRQoL domains within 18 months of the end of treatment, except for cognitive functioning. By contrast very few patients showed HRQoL impairment. HL survivors scores are similar to the general population matched for age and sex.	12
Hjermstad et al. 2006. Norway[26]	475	Mean: 46 SD: 11.6 Range: 21-74	Chemotherapy, radiotherapy, or combined therapy	195 months (53-431)	Cross-sectional	SF-36	Yes, comparison with nationally representative general practitioner data	No	No	Overall, HL survivors reported lower HRQoL than the general population. Survivors scored significantly worse on bodily pain, general health, (role) physical functioning, and social functioning.	11
Joly et al. 1996. France[27]	93	Mean: 42 Range: 23-85	Chemotherapy, radiotherapy, or combined therapy	Mean= 10 years (range 4-17)	Cross-sectional	EORTC-QLQ-C30	Yes, case control	No	Yes	Compared to controls, HL patients reported more physical, role, and cognitive functioning impairments, as well as dyspnoea and chronic fatigue, while no statistical difference was found in global health status.	10

Table 2. Overview of studies on HRQoL among Hodgkin's lymphoma survivors. (Continued)

Study, year, country	N	Mean age, SD or range	Treatment	Time since diagnosis	Design	Quality of life instruments	Comparison norm population	Evaluation treatment effect	Evaluation other characteristics	General conclusions	Quality score*
Mols et al. 2006. NL[28]	132	Not reported	Chemotherapy, radiotherapy, or combined therapy	Mean= 5-15 years	Populltion-based, cross-sectional	SF-36	Yes, comparison with an aged matched normative sample	Yes	Yes	HRQoL among HL survivors is lower compared to an age-matched normative sample. Survivors scored worse on general health, vitality, social functioning. No differences between treatments were reported.	11
Norum et al. 1996. Norway[29]	42	Not reported	Chemotherapy, radiotherapy, or combined therapy	16-20 months	Cross-sectional	EORTC-QLQ-C30	No	Yes	Yes	HL survivors reported a low frequency of symptoms and a high level of functioning. Survivors treated with mantle field irradiation and males seem to be at higher risk.	8
Van Tulder et al. 1994. NL[30]	81	Mean: 47 SD:11 Range: 25-77	Radiotherapy versus Combined therapy	Mean= 14 years (10-18)	Cross-sectional	SF-36	Yes, comparison with hospital visitors matched for age and sex	No	No	Self-reported HRQoL of HL survivors is still affected 10 to 18 years after treatment. In particular, physical and role functioning, sexuality, and overall health perceptions appear to be compromised.	10
Wettergren et al. 2003. Sweden[31]	121	Mean: 47 SD: 11.9	Chemotherapy, radiotherapy, or combined therapy	Mean= 14 years	Cross-sectional	SEIQoL-DW[3]	Yes, comparison with a random sample of Swedish citizens	No	Yes	Neither the current status in the different areas nor the HRQoL index score differed between HL survivors and controls. Thoughts and worries around disease, fatigue and loss of energy and late effects on skin and mucous membrane were the most commonly reported problems following HL.	11
Wettergren et al. 2004. Sweden[32]	121	Mean: 47 Range: 23-75	Chemotherapy, radiotherapy, or combined therapy	Mean=13 years (6-24)	Cross-sectional	SEIQoL-DW and SF-12	Yes, comparison with a random sample of Swedish citizens	Yes	Yes	The HRQoL of survivors who have survived a median of 14 years with HL is similar to that of controls, except for physical functioning.	11

Note. [1]SF-36= RAND-Short Form-36; [2]EORTC-QLQ- C30= European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; [3]SEIQoL-DW= Schedule for the Evaluation of Individual Quality of Life – Direct Weighting; *Maximum score of methodological quality is 12; NL= The Netherlands

Table 3. Overview of studies on HRQoL among non-Hodgkin's lymphoma survivors.

Study, year, country	N	Mean age, SD or range	Treatment	Time since diagnosis	Design	Quality of life instruments	Comparison (norm) population	Evaluation treatment effect	Evaluation other characteristics	General conclusions	Quality score*
Bellizzi et al. 2009. USA[33]	319	Mean: 60 SD: 14.9	Chemotherapy, chemotherapy + radiation, transplantation	2-6 years	Cross-sectional	SF-36[1]	Yes , survivors who met public health guidelines to those who were sedentary	No	Yes	NHL survivors who met public health guidelines reported better HRQOL than those who were sedentary.	11
Doorduijn et al. 2005. NL[34]	132	Mean: 72 Range: 65-84	CHOP versus CHOP+G-CSF Chemotherapy	Up till 18 months	Prospective	EORTC-QLQ- C30[2]	No	Yes	Yes	HRQoL was significantly better for NHL survivors in complete response or partial remission than for NHL survivors with progression/relapse.	12
Jerkeman et al. 2005 Norway[17]	95	Mean: 46 Range: 18-67	CHOP versus MACOP-B chemotherapy	Circa 13 months	Prospective	EORTC-QLQ-C30	Yes, comparison with an age- and sex adjusted reference population sample	Yes	Yes	Before treatment, NHL survivors exhibited lower scores of global HRQoL, physical, role and social functions, and more appetite loss, compared to the reference population. Role functioning improved compared to baseline, but remained depressed compared to the reference group more than 8 months after end of treatment.	12
Merli et al. 2004. Italy[35]	91	Mean: 73 Range: 66-85	Mini-CEOP versus P-VEBEC chemotherapy	Circa 2 months	Prospective	EORTC-QLQ-C30	No	Yes	Yes	The improvement of HRQoL at the end of treatment demonstrated that the symptoms of the disease have a greater negative influence on the NHL survivors' life than do the side effects of therapy.	10
Mols et al. 2007. NL[11]	294	Mean: 55	Chemotherapy, radiotherapy, or combined therapy	5-15 years	Cross-sectional	SF-36	Yes, comparison with an aged matched normative sample	Yes	Yes	From 5 to 15 years after diagnosis, the general health perceptions and vitality levels of NHL survivors remained significantly lower than those over their peers in the general population.	11

Table 3. Overview of studies on HRQoL among non-Hodgkin's lymphoma survivors. (Continued)

Study, year, country	N	Mean age, SD or range	Treatment	Time since diagnosis	Design	Quality of life instruments	Comparison (norm) population	Evaluation treatment effect	Evaluation other characteristics	General conclusions	Quality score*
Pettengell et al. 2008. UK[36]	222	Mean: 60 SD: 10.3	Off chemotherapy versus on chemotherapy	Not in article	Cross-sectional	FACT-General, FACT[3]-Lymphoma	Yes, comparison between disease stages	Yes	Yes	Patients with relapsed disease had the lowest scores on several HRQoL dimension. Furthermore, they compared patients on and of chemotherapy and they found that participants receiving chemotherapy were reporting worse on the overall HRQoL scale.	9
Reeve et al. 2009. USA[37]	53	Not in article	Surgery, radiation, chemotherapy, bone marrow/ stem cell transplantation, biologic therapy	2 years	Prospective	SF-36	Yes, comparison with matched control subjects without cancer	No	No	NHL survivors reported significant declines in physical and mental health compared with the control subjects.	11
Smith et al. 2009. USA[39]	761	Mean: 63 SD: 13.4	Surgery, radiation, chemotherapy, bone marrow/ stem cell transplantation, biologic therapy	2-44 years	Cross-sectional	SF-36, FACT-Lymphoma	Yes, comparison with general population-based norms	No	Yes	NHL survivors with active disease demonstrated worse physical and mental health functioning, worse HRQoL, and less positive and more negative impacts of cancer compared with disease-free survivors. No significant differences were observed between STS and LTS.	11
Smith et al. 2010. USA[38]	652	Mean: 63 SD: 13.5	Surgery, radiation, chemotherapy, bone marrow/ stem cell transplantation, biologic therapy	2-44 years	Cross-sectional	SF-36, FACT-Lymphoma	No	No	Yes	Younger NHL survivors reported better physical but worse mental health.	11
Vallance et al. 2005. Canada[40]	438	Mean: 61 SD: 13.1	Chemotherapy, radiotherapy, or combined therapy	Mean= 62 months	Cross-sectional	FACT-General	No	No	Yes	NHL survivors meeting public health exercise guidelines on and of treatment reported higher current HRQoL than those survivors not meeting guidelines.	11

Note. [1]SF-36= RAND-Short Form-36; [2]EORTC-QLQ-C30= European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; [3]FACT: Functional Assessment of Cancer Therapy; NL= the Netherlands; *Maximum score of methodological quality is 12.

Symptoms: HL survivors vs. normative samples

Clinically important worse scores of HL survivors were reported on several symptoms: cognitive problems[15, 22, 27], financial difficulties[15, 22, 24], fatigue/vitality[9, 15, 22 15, 22], dyspnea [22, 27] and insomnia[15, 22] were reported most often. Diarrhoea[22] and pain[26] were reported by one study each. Three studies found no clinically important differences between HL survivors and normative samples[9, 13, 30].

Treatment and HRQoL in HL survivors

One prospective study among 247 early stage HL survivors[23], found clinically important lower scores on vitality among patients treated with a combination of radiotherapy and chemotherapy compared to patients treated with radiotherapy alone, but only in the first year after treatment. This effect was also found in a cross-sectional study among 126 HL survivors in Austria[25]. They reported that patients treated with a combination of radiotherapy and chemotherapy showed clinically important lower scores on physical functioning and clinically important higher scores on pain, fatigue and dyspnoea compared to patients who were treated with radiotherapy or chemotherapy alone. Two small cross-sectional studies also found clinical important higher scores on dyspnoea. One found that 26 patients treated with mantle field irradiation reported higher scores compared with patients treated without (n=16)[29]. The other study found that 37 patients treated with high dose chemotherapy and stem cell transplantation reported higher scores compared with patients treated with conventional chemotherapy (n=61)[22]. Another prospective and four cross sectional studies found no effect of treatment on HRQoL[9, 16, 24, 28, 32].

Socio-demographic and clinical characteristics in HL survivors

Three cross-sectional and one prospective study observed that older patients reported clinically important worse outcomes[9, 16, 24, 27]. Six studies reported contradicting differences in HRQoL according to gender [9, 15, 16, 24, 27, 29], three studies found clinically important worse scores for women [9, 24, 27], one found only statistically worse scores for women[16], one found worse scores for men[29], and one found no differences[15]. Two cross-sectional studies reported that more advanced disease stage or recurrences were associated with reduced HRQoL, however no information about clinically important differences could be obtained[15, 32]. One study found remarkably that patients with stage IB-IIB scored significantly and clinically important lower on physical functioning and physical role limitations compared to patients with stage IA-IIA, IIIA-IVA, and IIIB-IVB[9].
The impact of length of survival on HRQoL was reported in a cross-sectional study, showing that patients who had survived 10-15 years after diagnosis reported clinically important higher HRQoL scores than patients who had survived 5-9 years[28].

Non-Hodgkin's lymphoma

HRQoL domains: NHL survivors vs. normative samples

In a prospective study among 95 Norwegians[7], patients showed clinically important lower scores on physical functioning up till 5 months after start of therapy compared to the normative sample. However, 8 months after end of treatment the difference was no longer clinically relevant. A Dutch cross-sectional study among 294 survivors[11], and an American cross-sectional study of 319 survivors found no clinically important lower scores for survivors compared to the normative

sample on physical functioning[33]. A cross-sectional study of 761 survivors[39] showed clinically important lower scores on the physical component scale. Another prospective study found statistically lower scores two years post-diagnosis, however no information about clinically important differences could be obtained[37].
A prospective study[17], exhibited clinically important lower scores on social functioning up till 6 months after start of therapy compared to the reference population. However, 8 months after end of treatment the difference was no longer clinically relevant. Two years post-diagnosis another prospective study found statistically lower scores, however no information about clinically important differences could be obtained[37]. A cross-sectional study found no clinically important differences with respect to social functioning[11].
A prospective study[17] showed clinically important lower scores on role physical function compared to the general population and these scores remained clinically important lower until the end of the study (8 months). Another prospective study found statistically lower scores two years post-diagnosis, however no information about clinically important differences could be obtained[37]. However, a cross-sectional study found no clinically important differences regarding role physical function[11].
Two prospective and a cross-sectional study did not find statistically or clinically important differences with respect to emotional functioning between NHL survivors and the normative populations[11, 17, 37].
A prospective study[17] exhibited clinically important lower scores on global health state up till 5 months after start of therapy compared to the reference population. However, 8 months after end of treatment the difference was no longer clinically relevant.
In addition, a cross-sectional study among 294 survivors showed clinically important lower scores on general health[11]. A prospective study found statistically lower scores two years post-diagnosis, however no information about clinically important differences could be obtained[37].
Three cross-sectional studies did not find clinically important differences between NHL survivors and the reference population on mental health[11, 33, 39].

Symptoms: NHL survivors vs. normative samples
A prospective study[17] showed clinically important lower scores on appetite loss, constipation, fatigue and dyspnoea up till respectively 3 months for the first 2 symptoms and 5 months for the last 2 symptoms after start of therapy compared to the reference population. However, 8 months after end of treatment the difference was no longer clinically relevant. Furthermore, they found that 9 months after the end of treatment until the end of the study, survivors had clinically more financial difficulties than the normative sample. A cross-sectional and prospective study found statistically lower scores for survivors on vitality[28,37], clinically important differences were only found by the cross-sectional study[28].

Treatment and HRQoL in NHL survivors
Three prospective studies showed no significantly different outcomes regarding HRQoL between patients treated with different chemotherapy regimens[17, 34, 35]. Two cross-sectional studies found that, compared to patients who did not receive chemotherapy, patients who did receive

chemotherapy experienced clinically important worse overall health functioning[36] and social well being[11].

Socio-demographic and clinical characteristics in NHL survivors
A prospective study did not found a relation between age and HRQoL outcome[17]. One cross-sectional study[11] found that older patients scored significantly lower on physical functioning than younger patients, however no information about clinically important differences could be obtained. Another cross-sectional study found clinical meaningful worse physical HRQoL scores for survivors who were older at study enrolment[38].
Two prospective studies[34, 35] found that survivors with progressive disease had clinically meaningful lower HRQoL than patients who were free of disease. Another prospective study found no relation between disease stage and HRQoL[17]. Two cross-sectional studies found statistically lower HRQoL score for survivors with active (relapsed) disease compared to disease free survivors[36, 39], clinically important differences were found in one of them[36].
The impact of length of survival was reported in a cross-sectional study[11] showing that patients who had survived 10-15 years after diagnosis reported clinically important higher HRQoL scores than patients who had survived 5-9 years, but this was not observed by another study[39] that compared short-term (2-5 years after diagnosis) and long-term (≥5 years after diagnosis) survivors.
Two prospective studies[34, 35] investigated HRQoL in elderly patients in relation to the age-adjusted International Prognostic Index which comprises 3 factors (performance status, lactate dehydrogenase, and stage)[45]. These studies found that patients with a low age-adjusted International Prognostic Index had a clinically meaningful better HRQoL than patients with a high age-adjusted International Prognostic Index. One prospective study found no relation between International Prognostic Index and HRQoL[17].
Two cross-sectional studies found that survivors meeting public health exercise guidelines reported a clinical meaningfully better mental and physical health[33, 40] than survivors not meeting these guidelines. Even more important, one of these studies[33] found that there was a significant dose-response pattern in which more exercise resulted in better mental and physical health.

DISCUSSION

This systematic review summarized and evaluated the results of studies focusing on the HRQoL of HL and NHL survivors. It is a remarkable fact that the majority of these studies concerned HL and not NHL, certainly in view of the number of patients being treated (8,500 vs. 65,000), or the number of survivors (165,000 vs. 440,000)[5]. Another point is that the first included study on HRQoL in HL was published in 1994, whereas all included studies on HRQoL in NHL were published after 2004.

The quality scores of the included HL studies ranged from 8 till 12 points, which indicates a high methodological quality. The shortcomings of these studies were mainly the lack of a prospective design and lack of information on non-respondents. The HRQoL domains that were affected the most in these patients and represent clinically important differences to patients were

(role) physical, social and cognitive functioning, general health, fatigue and financial problems and fewer dyspnoea and insomnia. Clinically important differences in emotional functioning, diarrhoea and pain were reported once. No clinically important differences were found in the included studies for physical functioning and mental health. Based on the studies included in this review, HL survivors who received a combination of chemotherapy and radiotherapy[23, 25], had worse scores on HRQoL domains. A clinically important higher score on dyspnoea was found by all therapies and this suggests that treatment in general results in problems[29]. However, most of the studies found no differences. In addition, HL survivors with older age and females reported worse outcomes. As expected, patients with a longer survival time reported better outcomes compared to those more recently diagnosed.

With respect to the included NHL studies, it was not possible to divide the results section in aggressive and indolent lymphomas due to lack of information within most available studies. The quality scores of NHL studies ranged from 9 till 12 points, which indicates a high methodology quality. The shortcomings were mainly a lack of a prospective design. The HRQoL domains that were affected the most in NHL survivors and represent clinically important differences to patients were physical functioning, appetite loss, vitality and financial problems. Clinically important differences in social functioning, role physical functioning and global health were mentioned once up till 5 months after treatment but waned over time. When comparing different chemotherapy regimens, no differences were reported. Nevertheless, having had chemotherapy was associated with clinically important lower scores on social well being[11] and overall health functioning[36] as reported by two cross-sectional studies in (long-term) cancer survivors. Interestingly, the effect of exercise was studied in NHL patients, whereas this has not been investigated in HL survivors. NHL survivors that met public health exercise guidelines reported a clinically important better HRQoL than survivors that did not meet exercise guidelines[33, 40], and even more important, more exercise resulted in a better mental and physical health[33]. Most studies showed worse HRQoL for survivors with aggressive disease or partial response, no response or progressive disease[34-36, 39], and those with a high age adjusted Prognostic Index[34, 35], which is well understandable.

The criterion of clinically important differences is very important to specify those domains of HRQoL that are affected in survivors. Most of the included studies based their conclusions only on statistical significance. Sometimes differences between survivors and comparative groups were statistical significant, but not clinically important for patients. Therefore, researchers should always use a criterion for the interpretation of clinical relevance instead of only evaluating the statistical significance to really attribute to the care of patients. Of the 17 included studies that compared HRQoL between survivors and a normative population, only seven[9, 15-17, 28, 32, 39] studies used a criterion to determine clinically relevant differences.

When comparing different studies, certainly in the field of HRQoL, there are many limitations. Seventeen of 22 included papers had a cross-sectional design[9, 11, 15, 24-33, 39, 40]. A limitation of this methodology is that it is not possible to draw causal relationships. In addition, these studies may have survivorship bias, because patients that do relatively worse will not participate as they are too ill or dead. A prospective design study provides better relevant answers about causality, for

example the temporal direction between treatment and HRQoL, but only five studies had this design. Also the lack of information in some studies on non-respondents or possible bias makes it more difficult to determine the trustworthiness of a study. Future studies should therefore always try to collect data on non-respondents or discuss the possible risk of bias. Although there are inherent relationships between HRQoL dimensions, we discussed the dimensions separately to identify which specific dimensions are most affected. This does not mean that the unmentioned dimensions could not be affected. However, the underlying mechanisms between the relations in HRQoL dimensions and symptoms is understudied and not yet clear. Therefore studies focusing on symptom clustering are needed.

The different HRQoL questionnaires used, predominantly the EORTC QLQ-C30 (disease specific questionnaire) and the SF-36 (generic questionnaire) made it difficult to compare results, as the various scales do not exactly measure the same HRQoL dimensions. The questionnaires in the included studies were almost all generic or disease specific. Generic questionnaires are designed to measure health in general, and are therefore appropriate for a wide range of patient groups and also the general population, but are less sensitive to detect certain aspects of disease and treatment that are relevant to a specific patient group. The EORTC QLQ-C30 is a disease specific questionnaire, but consists of such questions that this questionnaire is also applicable to the general population[46]. In addition to these generic and disease specific questionnaires, lymphoma specific questionnaires should be used to detect, with more sensibility, side-effects and symptoms particularly relevant to HL and NHL survivors. However, cancer specific questionnaires are relatively new and underdeveloped and therefore used infrequently. Only two studies[36, 39] used a lymphoma specific questionnaire, the FACT-Lymphoma, which was developed in 2004[44].

The American Cancer Society defines ‘long-term survivors’ as every person who is still alive five years after diagnosis[47]. Six studies, five HL[15, 28, 30-32] and one NHL[11], focused on patients who had survived more than five years. Only one recent study focused on the longitudinal HRQoL of HL survivors[16]. Especially these kind of studies are important in view of the growing number of survivors to identify as soon as possible negative long-term effects, certainly when taken in consideration the implementation of new treatments.

If we compare the results of the eleven cross-sectional and two prospective studies among HL survivors, some cross-sectional studies are consistent with the prospective studies on points as comparison with the norm population, relation with received treatment and socio-demographic and clinical differences. However, if we compare the two prospective HL studies, one[23] did find a relation with treatment while the other[16] did not. With respect to NHL studies, again some of the cross-sectional studies (four) are consistent with the prospective ones. However, if we compare the three prospective studies, only consistent results concerning the absence of the relation with treatment on HRQoL were found[17, 34, 35].

In conclusion, the reviewed literature about the HRQoL of HL and NHL survivors reflects that several domains, even in long-term survivors, are affected. Overall, HL survivors experience the most problems in (role) physical, social and cognitive functioning, general health, fatigue

and financial problems. In addition, HL survivors with older age and female sex reported worse outcomes. NHL survivors experience the most problems in physical functioning, appetite loss, vitality and financial problems. However, these results are less clear as only a limited number of studies are performed among NHL survivors. Furthermore, importantly the HRQoL in NHL survivors not meeting public exercise guidelines is low, but can be improved with more exercise. More research on the longitudinal comparison between HL and NHL survivors and healthy controls should be performed. Lymphoma specific questionnaires should be further developed to better understand in detail the side-effects of treatment on HL and NHL survivors.

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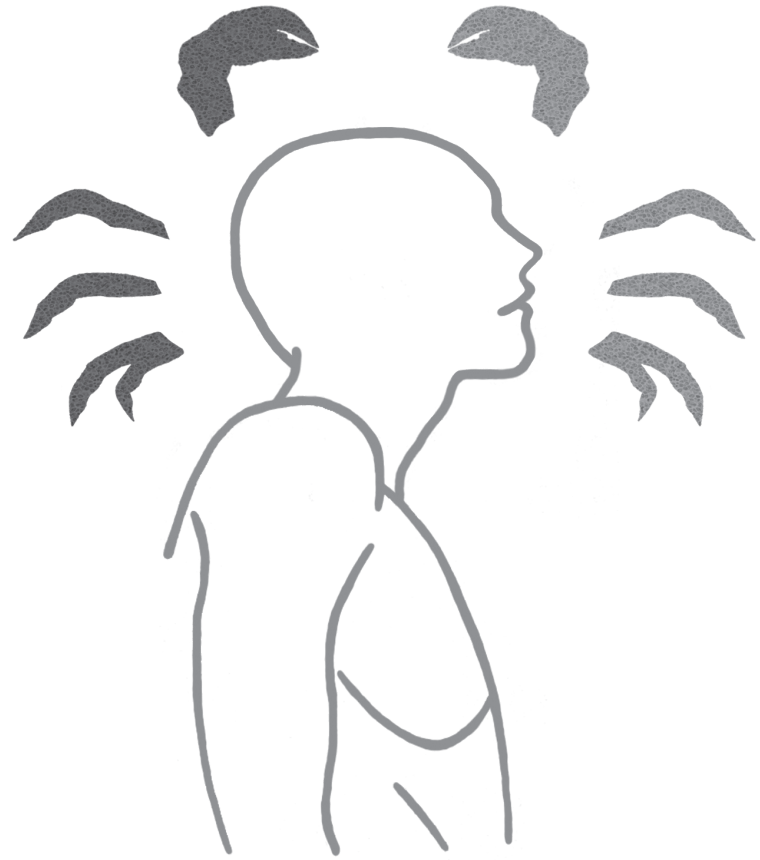
CHAPTER 3

Health-related quality of life and persistent symptoms in relation to (R-)CHOP14, (R-)CHOP21 and other therapies among patients with diffuse large B-cell lymphoma: results of the population-based PHAROS-registry



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ABSTRACT

Purpose
The increasing number of longer living patients with diffuse large B-cell lymphoma (DLBCL) and serious side effects of treatment, urged us to study the health-related quality of life (HRQoL) and persistent (treatment-related) symptoms in unselected patients after different treatment modalities and compare HRQoL of patients with a normative population.
Methods
The population-based Eindhoven Cancer Registry was used to select all patients diagnosed with DLBCL from 2004-2010. The EORTC QLQ-C30 was completed twice, with a one-year interval. Detailed data on treatment were extracted from the Population-based HAematological Registry for Observational Studies.
Results
256 patients responded (84%, T1). Compared to patients treated with (R-)CHOP21, those who underwent (R-)CHOP14 more often reported tingling in hands and feet (27% versus 42%, p=0.02), fatigue (35% versus 46%, p=0.03) and reported a lower global health status/HRQoL. Mean HRQoL was statistically and clinically relevantly lower among DLBCL patients compared to a normative population (p<0.01). Persistent tingling in hands/feet was reported more often by older patients and patients treated with (R-)CHOP14 independently of the other characteristics. Furthermore, patients who reported symptoms exhibited significantly lower HRQoL compared to patients without symptoms/worries.
Conclusion
Patients treated with (R-)CHOP14 reported more neuropathic symptoms, more fatigue and a lower HRQoL than patients treated with (R-)CHOP21. Alertness for persistent symptoms that occur during and after treatment of DLBCL patients is needed and may help to avoid lasting negative influence on their HRQoL.

INTRODUCTION

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of malignancies and is the most common hematologic malignant neoplasm in adults. In the United States, there were approximately 510,000 people alive who had a history of NHL on January 1, 2010[1], and the ten-year prevalence of aggressive NHL in the Netherlands, with 6,570 patients in the year 2009, is expected to increase to approximately 10,600 patients in 2020[2]. Diffuse Large B-Cell Lymphoma (DLBCL) is the most common subtype, accounting for approximately 30-40% of NHL[3, 4].

Traditionally, treatment of DLBCL included the CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen[5]. With the addition of rituximab (R), response rates and overall survival have improved significantly, defining rituximab combined with CHOP (R-CHOP) as the new standard treatment for patients with DLBCL[3, 6, 7] whereby CHOP every 14 days seemed superior to a 21-day schedule, with respect to overall survival[8]. However recently, two studies showed that overall survival in patients treated with R-CHOP14 was not superior to patients treated with R-CHOP21[9, 10]. Patients with recurrent disease are treated with high-dose chemotherapy (HDCT) combined with autologous stem cell transplantation (ASCT).

The increasing number of DLBCL patients that are being treated with changing treatment regimens requires careful evaluation not only of survival improvements, but also regarding potential side effects of treatment, and (long-term) health-related quality of life (HRQoL). HRQoL is a multidimensional construct that covers patients' perceptions of his or her physical, emotional, social and cognitive functions and disease and/or treatment related symptoms and represents patients' subjective experience with cancer.
Up to now, some studies have investigated HRQoL among aggressive lymphoma patients[11-13] and a few among DLBCL patients[14, 15], however most studies were randomized clinical trials, or had a cross-sectional design. As a consequence, elderly patients and patients with comorbidities were underrepresented or HRQoL was only assessed at one time point. Furthermore, a comparison of (long-term) HRQoL between patients treated with (R-)CHOP14 or (R-)CHOP21 has never been made.

The aims of the present study were therefore to (1) evaluate (long-term) HRQoL and symptoms/worries of DLBCL patients on two time points in a population-based setting that includes these previously underrepresented patients and compare them with an age-and sex-matched normative population, (2) compare HRQoL and symptoms/worries between patients treated with (R-)CHOP14 or (R-)CHOP21 up to five years post-treatment, and (3) assess the prevalence of persistent symptoms/worries and identify associated clinical and/or socio-demographic characteristics. We hypothesized that HRQoL would be deteriorated in patients compared to the normative population. We furthermore hypothesized that patients treated with (R-)CHOP14 would report a lower HRQoL and more symptoms than patients treated with (R-)CHOP21.

METHODS

Setting and population

This study took place within the scope of the Population-based HAematological Registry for Observational Studies (PHAROS), an extension of the Netherlands Cancer Registry (NCR). The NCR was used to select all patients, who were diagnosed with DLBCL as defined by the International Classification of Diseases for Oncology-3 codes (ICD-O-3)[16] between January 1, 2004 and December 31, 2010 in an area covering approximately 40% of the Dutch population. The NCR-data of these patients (including date of diagnosis, morphology, gender, date of birth and stage) were replenished with details on treatment, adverse events and treatment outcomes from PHAROS.

Additionally, a longitudinal population-based survey was set up among DLBCL patients registered with the Eindhoven Cancer Registry (ECR) which fills about 15% of NCR. The database with patients diagnosed between January 1, 2004 and December 31, 2010 was linked with the database of the Central Bureau for Genealogy to exclude patients who were deceased. HRQoL and symptoms were collected within PROFILES (Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship). PROFILES is a registry for the study of the physical and psychosocial impact of cancer and its treatment from a dynamic, growing population-based cohort of both short and long-term cancer survivors[17].

Questionnaires were sent out in batches and this was done on three time points. In May 2009, patients diagnosed between January 2004 and January 2009 were included in the study and received the first questionnaire. In November 2009 and May 2011 patients newly diagnosed after the last inclusion date were subsequently invited to participate (T1) to include all patients up to December 31, 2010. Patients received the subsequent questionnaire (T2) one year after T1. Ethical approval for the study was obtained from a certified Medical Ethics Committee (of the Maxima Medical Centre in Veldhoven, The Netherlands; number 0734).

Study measures

The Dutch validated version of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) was used to assess HRQoL[18]. Answer categories range from one (not at all) to four (very much). After linear transformation, all scales and single item measures range in score from 0 to 100. A higher score on function scales and global health and quality of life scale implies a better HRQoL, whereas for symptoms a higher score refers to more symptoms[18].

The Dutch version of the EORTC CLL-16 was used to assess disease and treatment-related specific symptoms and worries. This questionnaire was originally developed for patients with Chronic Lymphocytic Leukemia but is also applicable to lymphoma patients. The symptom tingling in hands/feet was added to this questionnaire, as it appeared from the literature and interactions with patients that this might be a prevalent symptom. Answer categories range from one (not at all) to four (very much).

Comorbidity at the time of survey was categorized according to the adapted Self-administered Comorbidity Questionnaire (SCQ)[19]. Patients' marital status and educational level were also assessed in the questionnaire. Clinical data was obtained from the NCR and PHAROS.

If patients received more than one treatment line, the treatment category was based on the sum of treatments before completion of the questionnaire and were ordered from most to least expected impact on HRQoL. 1: autologous stem cell transplantation (ASCT), 2: high-dose chemotherapy (HDCT), 3: (R-)CHOP14, 4: (R-)CHOP21, 5: other chemotherapy (CT), radiotherapy (RT) or no therapy.

Normative population

The normative population was selected from a reference cohort of 2040 individuals from the general Dutch population (CentER panel). The set of questionnaires completed by this normative population in November 2011 included the EORTC QLQ-C30, SCQ and data on socio-demographics. This cohort is considered representative for the Dutch-speaking population in the Netherlands[20]. Based upon this normative population an age- and sex-matched selection was made of 425 persons to compare HRQoL with the DLBCL patients. For matching, ten strata were formed using sex and age (5 categories). Within each stratum a maximum number of persons from the reference cohort were randomly matched according to the 'strata frequency distribution' of the patients. This resulted in 425 matched cancer-free panel members for 256 patients.

Statistical analyses

Differences in socio-demographic and clinical characteristics between respondents and non-respondents or patients with unverifiable addresses, between patients who completed one or two questionnaires, and between patients treated with (R-)CHOP14 or (R-)CHOP21 were compared with chi-square or t-tests, where appropriate.

The mean QLQ-C30 scores from the DLBCL patients were compared with the mean scores of an age- and sex-matched Dutch normative population using independent sample t-tests.

Analyses of covariance (ANCOVA) were carried out to compare the mean QLQ-C30 scores and logistic regression analyses were used to compare the prevalence of CLL-16 symptoms and tingling in hands/feet between patients treated with (R-)CHOP14 or (R-)CHOP21 adjusted for age, number of comorbidities, time since treatment, and number of treatment cycles. Logistic regression analyses were also used to compare the prevalence of CLL-16 symptoms per time since treatment category stratified per treatment (i.e. (R-)CHOP14 or (R-)CHOP21), adjusted for age and number of comorbidities. Symptoms/worries were dichotomized as present (answer categories 'a bit', 'quite a bit' or 'very much') or not present (answer category 'not at all').

Multivariate logistic regression analyses were constructed to investigate the independent association between socio-demographic and clinical variables and the five most frequently reported persistent symptoms/worries, and to assess the variance in the QLQ-C30 global health status/HRQoL scale explained by these symptoms/worries. Persistent symptoms/worries were defined by patients who had a specific symptom on both T1 and T2 and factors were a priori determined, including sex, age, number of comorbidities, time since diagnosis, stage, treatment and number of treatment cycles. Since we observed multi-collinearity between treatment and number of treatment cycles, we ran the analysis twice, once with treatment and once with number or treatment cycles.

Analyses of covariance (ANCOVA) were also carried out to compare the mean EORTC QLQ-C30 global health status/HRQoL scale between patients with or without persistent symptoms/worries adjusted for sex, age, number of comorbidities and time since diagnosis. Persistent symptoms were defined as symptoms present at both T1 and T2.
All statistical analyses were performed using SAS (version 9.3 for Windows; SAS Institute Inc., Cary, NC). P values of <0.05 were considered statistically significant. Clinically relevant differences were determined using the evidence-based guidelines for interpretation of the EORTC QLQ-C30 between groups[21]. Patients were determined to be fatigued with an QLQ-C30 fatigue score >21.9 (mean of age and sex matched normative population + small clinically important difference, i.e. 5 points).

RESULTS

Patients and normative population

Two hundred fifty-six DLBCL patients completed the first questionnaire (T1, 84% response rate; Figure 1) and subsequently, 130 patients completed the questionnaire again one year later (T2). The mean age at baseline survey completion was 63.5 years and 66% were male (Table 1). Mean time since diagnosis was 2.6 years and 93% of patients underwent one treatment line. (R-)CHOP14 was received by 37% and (R-)CHOP21 by 50% of patients, the other 13% was treated with SCT, HDCT, other or no therapy. Two-third of patients reported one or more comorbid conditions, the most common were arthritis, back pain and hypertension. Patients treated with (R-)CHOP21 were older, more often diagnosed with stage I, and had a longer time since diagnosis and time since treatment compared to patients treated with (R-)CHOP14.
With respect to the age- and sex matched normative population, mean age at baseline survey completion was 63.7 years and 66% was men. Almost two-third (66%) of respondents reported one or more comorbid conditions, the most common were hypertension and back pain.

Quality of data

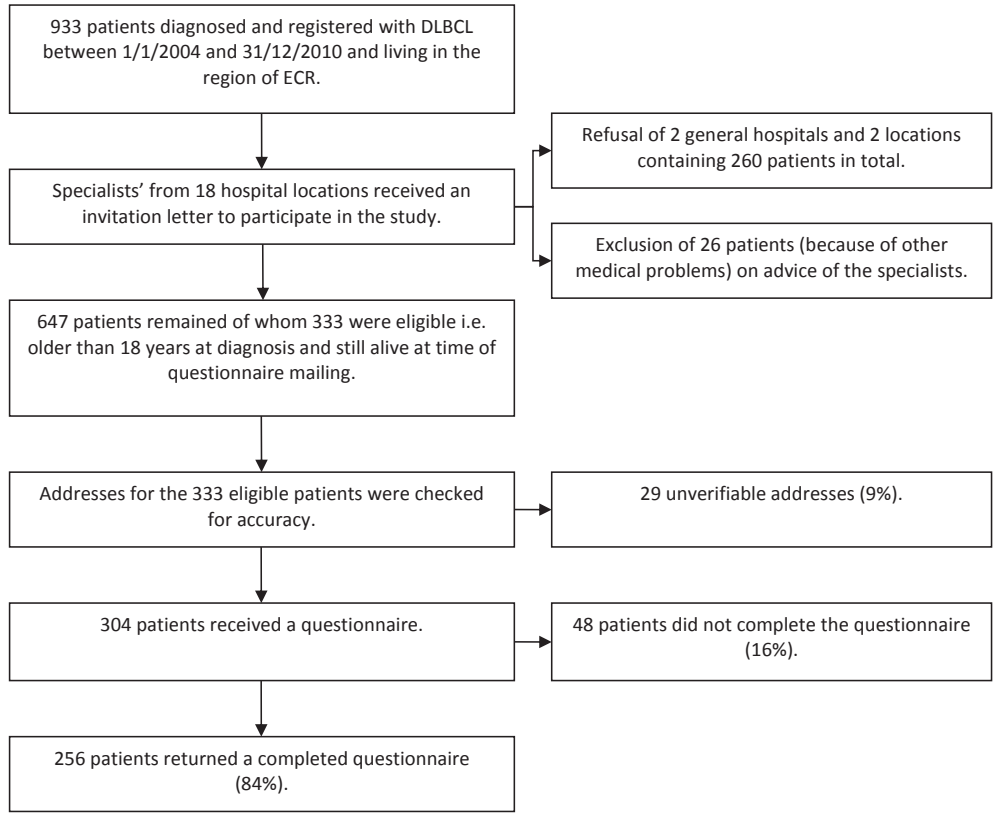
Non-response analysis

At baseline, non-respondents (N=48) and patients with unverifiable addresses (N=29) were more often female than respondents (60% and 66% versus 34%; p<0.01) and non-respondents were more often treated shorter than 12 months ago compared to respondents (48% versus 27%; p=0.01). No statistically significant differences between these groups were observed for age, time since diagnosis, stage, treatment and number of treatment lines (data not shown).

Analysis between patients who completed one or more questionnaires

No statistically significant differences were observed between patients who completed one and patients who completed two questionnaires for QLQ-C30 global health and QoL score ($\overline{X}$ =74.8 versus $\overline{X}$ =72.9, p=0.47) or for sex, age, stage, (time since) treatment, comorbidities, marital status and educational level (data not shown).

Figure 1. Flow chart of the data collection process.



Note. DLBCL=Diffuse Large B-Cell Lymphoma, ECR=Eindhoven Cancer Registry.

HRQoL of DLBCL patients and the normative population

Compared to an age- and sex-matched normative population, responding DLBCL patients exhibited on average statistically significant and clinically relevant worse scores on QLQ-C30 physical, role, cognitive and social functioning. DLBCL patients also reported more fatigue, dyspnea, sleeping problems, appetite loss, and financial problems compared to the matched norm (all p<0.05 and small clinically important differences; Figure 2).

HRQoL and symptoms/worries in relation to treatment

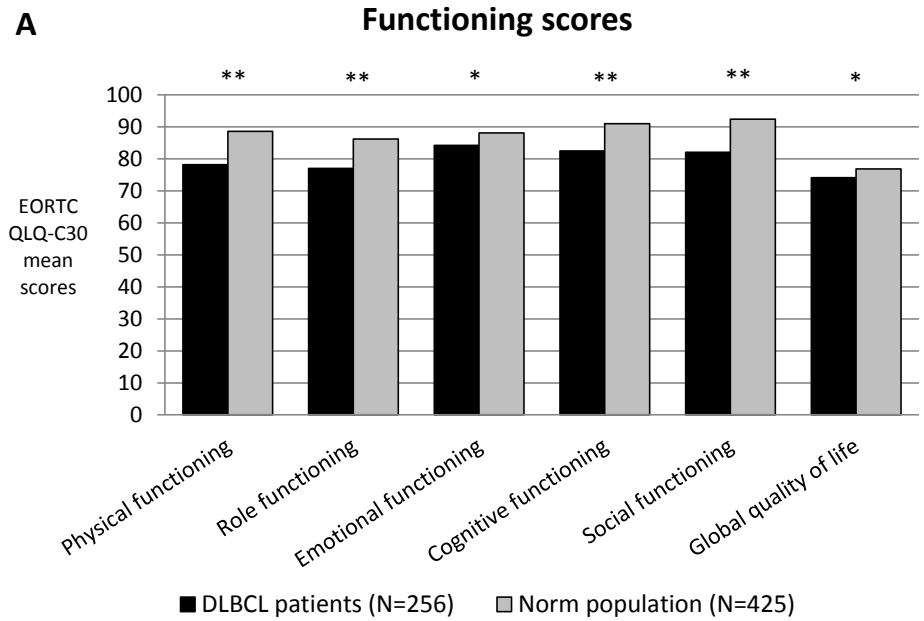
Patients treated with (R-)CHOP14 reported significantly more often tingling in hands and feet compared to patients treated with (R-)CHOP21 (42% versus 27%, p=0.02; adjusted for age, number of comorbidities, time since treatment and number of treatment cycles). Patients treated with (R-)CHOP14 also reported a statistically significant lower global health status/quality of life compared to patients treated with (R-)CHOP21 (p=0.04; Table 2). Furthermore, significantly more patients with fatigue were identified in the (R-)CHOP14 group (46%) compared

Table 1. Clinical and socio-demographic characteristics of the total group of responding patients (N=256) and according to treatment regimen.

	Total	Patients treated with HDCT ± ASCT, other CT, RT or no therapy	Patients treated with (R-)CHOP14	Patients treated with (R-)CHOP21	(R-)CHOP14 versus (R-)CHOP21
	N=256	N=33	N=95	N=128	
	N (%)	N (%)	N (%)	N (%)	p-value
Gender					0.80
Male	169 (66)	26 (79)	60 (63)	83 (65)	
Female	87 (34)	7 (21)	35 (37)	45 (35)	
Age: mean (SD)	63.5 (13.4)	56.5 (15.1)	61.4 (13.2)	66.9 (12.0)	<0.01
<55 years	58 (23)	12 (36)	26 (27)	20 (16)	
55-65 year	70 (27)	12 (36)	27 (28)	31 (24)	
66-75 year	87 (34)	7 (21)	34 (36)	46 (36)	
75+ years	41 (16)	2 (6)	8 (8)	31 (24)	
Years since diagnosis at time of questionnaire completion: mean (SD)	2.6 (1.3)	2.8 (1.5)	2.0 (1.1)	2.9 (1.2)	<0.01
Months since treatment at time of questionnaire completion: median	21.0	24.0	16.3	29.2	<0.01
0-24 months since treatment	131 (51)	12 (36)	64 (67)	55 (43)	
24+ months since treatment	112 (44)	11 (33)	29 (31)	72 (56)	
Missing	13 (5)	10 (30)	2 (2)	1 (1)	
Number of treatment lines					0.16
1st treatment line	228 (89)	14 (42)	91 (96)	123 (96)	
Subsequent treatment line	17 (7)	8 (24)	4 (4)	5 (4)	
Missing	11 (4)	11 (33)	0 (0)	0 (0)	
Number of treatment cycles					<0.01
< 6 cycles	NA	NA	12 (13)	35 (27)	
≥ 6 cycles	NA	NA	82 (86)	92 (72)	
Missing			1 (1)	1 (1)	
Stage at diagnosis					<0.01
I	85 (33)	15 (45)	15 (16)	55 (43)	
II	60 (23)	6 (18)	21 (22)	33 (26)	
III	56 (22)	6 (18)	31 (33)	19 (15)	
IV	53 (21)	6 (18)	26 (27)	21 (16)	
Missing	2 (1)	0 (0)	2 (2)	0 (0)	
Self reported comorbidities					0.45
None	79 (31)	15 (45)	30 (32)	34 (27)	
1 comorbidity	83 (32)	9 (27)	32 (34)	42 (33)	
2 or more comorbidities	77 (30)	8 (24)	25 (26)	44 (34)	
Missing	17 (7)	1 (3)	8 (8)	8 (6)	
Marital Status					0.87
Partner	201 (79)	25 (76)	76 (80)	100 (78)	
No partner	51 (20)	8 (24)	18 (19)	25 (20)	
Missing	4 (2)	0 (0)	1 (1)	3 (2)	
Education level[$]					0.12
Low	41 (16)	2 (6)	14 (15)	25 (20)	
Medium	151 (59)	19 (58)	53 (56)	79 (62)	
High	60 (23)	11 (33)	27 (28)	22 (17)	
Missing	4 (2)	1 (3)	1 (1)	2 (2)	

Note. HDCT=High-Dose Chemotherapy, ASCT=Autologous Stem Cell Transplantation, CT=chemotherapy, RT=radiotherapy, (R-)CHOP=(Rituximab), cyclophosphamide, doxorubicin, vincristine, and prednisone. NA=Not Applicable. In the (R-)CHOP14 group, 2 patients were treated without rituximab and in the (R-)CHOP21 group 15 patients were treated without rituximab. [$]Education levels included low = no/primary school; medium = lower general secondary education/vocational training; or high = pre-university education/ high vocational training/ university.

Figure 2. Differences on EORTC QLQ-C30 mean functioning, global quality of life and symptom scores between DLBCL patients (N=256) and an age- and sex-matched normative population (N=425) at T1.



Note. *p<0.05; **p<0.05 and small clinically important differences [21]; A higher score on functioning scores implies a better health-related quality of life, whereas a higher score on symptom scores refers to more symptoms. EORTC QLQ-C30= European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30. DLBCL=Diffuse Large B-Cell Lymphoma.

Table 2. Differences between DLBCL patients treated with (R-)CHOP14, (R-)CHOP21, ASCT, HDCT or other CT, RT or no therapy on EORTC symptoms, worries and HRQoL at T1.

	Patients treated with (R-)CHOP14 N=95	Patients treated with (R-)CHOP21 N=128	(R-)CHOP14 versus (R-)CHOP21	Patients treated with HDCT ± ASCT, other CT, RT or no therapy N=33
EORTC CLL-16	N (%)	N (%)	p-value[1]	N (%)
Weight loss	18 (19)	16 (13)	0.29	3 (9)
Dry mouth	40 (42)	47 (38)	0.12	15 (47)
Bruises	8 (8)	9 (7)	0.86	4 (12)
Abdominal discomfort	31 (33)	40 (32)	0.94	8 (25)
Temperature up/down	14 (15)	16 (13)	0.91	2 (6)
Night sweats	27 (29)	44 (35)	0.58	8 (24)
Skin problems	37 (39)	55 (44)	0.66	15 (45)
Feeling ill or unwell	23 (24)	17 (13)	0.08	4 (12)
Feeling lethargic	33 (35)	39 (31)	0.08	8 (24)
Feeling slowed down	42 (44)	47 (37)	**0.03**	13 (39)
Limited in activities	32 (34)	37 (30)	0.15	12 (36)
Worried future health	55 (58)	60 (48)	0.05	20 (60)
Chest infections	14 (15)	19 (15)	0.17	9 (27)
Other infections	13 (14)	22 (17)	0.38	3 (9)
Repeated antibiotics	12 (13)	21 (17)	0.68	4 (12)
Worried about infections	22 (24)	27 (21)	0.62	9 (27)
Tingling hands/feet	40 (42)	34 (27)	**0.02**	9 (28)
EORTC QLQ-C30	Mean (SD)	Mean (SD)	p-value[1]	Mean (SD)
Physical Functioning	76.9 (22)	78.9 (21)	0.21	79.6 (23)
Role Functioning	75.1 (30)	79.4 (28)	0.16	73.2 (32)
Emotional Functioning	82.7 (19)	85.9 (19)	0.20	81.8 (22)
Cognitive Functioning	82.6 (23)	84.8 (20)	0.13	73.2 (28)
Social Functioning	80.7 (26)	84.4 (25)	0.21	77.3 (31)
Global health status/QoL	71.9 (22)	75.2 (19)	**0.04**	76.0 (18)
Fatigue	28.2 (27)	26.5 (26)	0.25	29.5 (27)
Nausea / Vomiting	5.6 (14)	4.1 (13)	0.55	2.5 (7)
Pain	18.4 (27)	14.4 (24)	0.22	14.1 (24)
Dyspnea	17.7 (28)	17.3 (26)	0.43	14.6 (22)
Insomnia	18.9 (29)	18.8 (29)	0.44	17.1 (22)
Appetite loss	13.0 (28)	8.6 (22)	0.19	1.0 (6)
Constipation	8.4 (23)	6.9 (19)	0.05	4.0 (14)
Diarrhea	7.4 (20)	5.6 (15)	0.13	2.0 (8)
Financial Problems	11.9 (22)	5.9 (17)	0.09	18.1 (32)
% Fatigued patients	46 %	35 %	**<0.01**	44 %

Note. HDCT=High-Dose Chemotherapy, ASCT=Autologous Stem Cell Transplantation, CT=chemotherapy, RT=radiotherapy, (R-)CHOP=(Rituximab), cyclophosphamide, doxorubicin, vincristine, and prednisone. EORTC QLQ-C30= European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30. DLBCL=Diffuse Large B-Cell Lymphoma; CLL-16=Chronic Lymphocytic Leukemia 16. [1]p-value is adjusted for age, time since treatment, number of treatment cycles, and number of comorbidities.
EORTC CLL-16 Symptoms/worries were dichotomized as present (answer categories 'a bit', 'quite a bit' or 'very much') or not present (answer category 'not at all'). Patients were fatigued if they had an EORTC QLQ-C30 fatigue score >23.1 (mean normative population + small clinically important difference, i.e. 5 points).

CHOP21 group (35%; p=0.03) and patients treated with (R)-CHOP14 also more often felt slowed down compared to patients treated with (R-) CHOP21 (44% versus 37%; p=0.03). No statistically significant differences were observed on the other HRQoL scales and symptoms. HRQoL scores and percentages of symptoms/worries of patients treated with HDCT, ASCT and other therapies are also displayed in Table 2, although numbers were too small to draw conclusions.

Prevalence of symptoms/worries

The most frequently reported symptoms/worries (by at least one-third of patients) on T1 were worry about future health (53%), skin problems (itching, dry skin; 42%), feeling slowed down (40%), dry mouth (40%), and tingling in hands and feet (33%). The prevalence of symptoms/worries did not significantly differ per time since treatment category, except for skin problems which occurred more often among patients who received treatment more than three years ago (Figure 3). Furthermore, worry about future health and having a dry mouth seemed to occur more often among patients until one year after treatment.

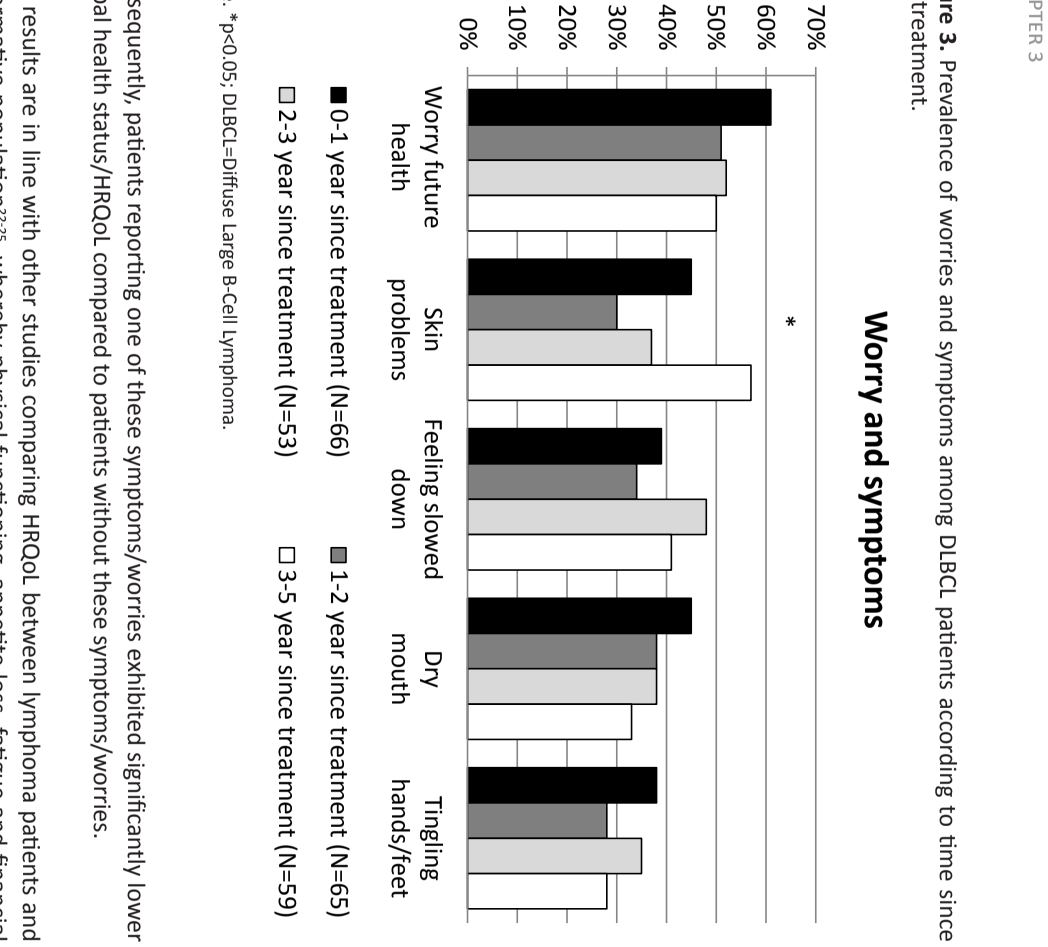
Factors associated with persistent symptoms/worries and the relation with HRQoL

Of the patients who completed the questionnaire again one year later (N=130), persistent symptoms/worries were reported by 20-33% of patients. Multivariate logistic regression analyses showed that older patients and patients treated with (R-)CHOP14 more often had persistent tingling in hands and feet compared to patients treated with (R-)CHOP21 independently of the other characteristics. Persistent worry about future health and a persistent slowed down feeling was reported more often by patients with comorbid diseases (Table 3). Persistent skin problems more often occurred among patients diagnosed longer ago. Sex, disease stage and number of treatment cycles were not associated with any of the persistent symptoms/worries. Although, it seemed that, when studying the crude percentages, after the eighth cycle of (R-)CHOP14 patients would report tingling in hands and feet more often compared to patients treated with less cycles (48% versus 32%) and for patients treated with (R-)CHOP21 the percentages were 30% versus 25%.
Subsequently, patients who reported to be persistently slowed down, worrying about future health or having tingling hands or feet had statistically significantly and clinically relevant lower EORTC global health status/HRQoL compared to patients without these persistent symptoms/worries (all p<0.01, data not shown).

DISCUSSION

HRQoL was lower among DLBCL patients compared to an age and sex-matched normative population, which confirms our hypothesis. Patients treated with (R-)CHOP14 reported tingling in hands and feet, fatigue, and slowed down feeling more often compared to patients treated with (R-)CHOP21. Patients treated with (R-)CHOP14 also reported a lower global health status/quality of life compared to patients treated with (R-)CHOP21. The five most frequently reported symptoms/worries by at least one-third of patients were worry about future health, skin problems, feeling slowed down, having a dry mouth and having tingling in hands/feet.

Figure 3. Prevalence of worries and symptoms among DLBCL patients according to time since last treatment.



Note. *p<0.05; DLBCL=Diffuse Large B-Cell Lymphoma.

Subsequently, patients reporting one of these symptoms/worries exhibited significantly lower global health status/HRQoL compared to patients without these symptoms/worries.

Our results are in line with other studies comparing HRQoL between lymphoma patients and a normative population[22-25], whereby physical functioning, appetite loss, fatigue and financial problems were most often affected. In the present study, also DLBCL patients treated >2 years ago were included, indicating that HRQoL is not only diminished at time of treatment but also thereafter.

Experiences of neuropathy among lymphoma patients were also observed by two other studies, although they did not compare patients treated with RCHOP14 versus RCHOP21. One small longitudinal study among 32 B-cell lymphoma patients treated with R-CHOP or R-CVP observed sensory neuropathy-associated symptoms among 84% and polyneuropathy among 44% of patients[26]. The other longitudinal study observed a significant increase in peripheral neuropathy after the 6th cycle of CHOP compared to baseline[11]. We observed no statistically significant difference in tingling hands and feet according to number of treatment cycles. Although it seemed that, when studying the crude percentages, after the eighth cycle of (R-)CHOP14 patients would report tingling in hands and feet more often compared to patients treated with less cycles. Further research should take this into account. An explanation for more

Table 3. Socio-demographic and clinical factors associated with five major persistent symptoms or worries among DLBCL patients (N=130).

	Persistent Tingling hands/feet			Persistent Worry future health			Persistent Skin problems			Persistent Slowed down feeling			Persistent Dry mouth		
	Odds ratio	95% CI	p-value	Odds ratio	95% CI	p-value	Odds ratio	95% CI	p-value	Odds ratio	95% CI	p-value	Odds ratio	95% CI	p-value
Sex (men=ref)	0.50	0.2-1.5	0.22	1.37	0.6-3.2	0.46	0.83	0.3-2.0	0.67	2.23	0.9-5.6	0.09	1.78	0.8-4.1	0.18
Age	1.08	1.0-1.1	0.02	0.98	0.9-1.0	0.33	0.99	0.95-1.0	0.79	0.97	0.9-1.0	0.14	1.03	0.99-1.1	0.13
Time since diagnosis	1.42	0.9-2.1	0.09	1.01	0.7-1.4	0.95	1.51	1.1-2.1	0.02	1.12	0.8-1.6	0.54	0.99	0.7-1.3	0.96
Comorbidity (no=ref)	1.42	0.4-5.1	0.59	4.44	1.4-14	0.01	2.14	0.7-6.3	0.17	7.99	1.6-40	0.01	1.11	0.4-3.0	0.84
Stage															
Stage I	Ref			Ref			Ref			Ref			Ref		
Stage II	4.13	0.9-19.1	0.07	1.90	0.7-5.5	0.24	0.97	0.3-3.0	0.96	0.54	0.1-2.0	0.35	1.04	0.4-3.0	0.94
Stage III	3.51	0.7-18.4	0.14	0.44	0.1-1.6	0.20	2.36	0.7-7.6	0.15	0.50	0.1-1.9	0.32	0.88	0.3-2.9	0.84
Stage IV	3.72	0.8-17.8	0.10	1.04	0.3-3.2	0.95	0.56	0.2-2.0	0.38	0.90	0.3-3.1	0.87	1.46	0.5-4.5	0.51
Treatment															
(R-)CHOP14	4.29	1.3-14.5	0.02	0.95	0.3-2.6	0.93	2.02	0.7-6.0	0.20	1.01	0.3-3.0	0.99	1.83	0.7-4.9	0.23
(R-)CHOP21	Ref			Ref			Ref			Ref			Ref		
Other[1]	0.47	0.05-4.8	0.52	1.47	0.4-5.7	0.58	0.97	0.2-4.2	0.97	0.25	0.03-2.2	0.21	1.54	0.4-6.1	0.54

Note. Ref=reference category; DLBCL=Diffuse Large B-Cell Lymphoma, (R-)CHOP=(Rituximab), cyclophosphamide, doxorubicin, vincristine, and prednisone. [1]Other treatment category consists of patients treated with HDCT, ASCT, other CT, RT or no therapy, CI= Confidence Interval.
Persistent symptoms were defined as a symptom was present on both T1 and T2.
We reran the analyses with number of treatment cycles instead of treatment, or instead of stage. These analyses did not show any statistically significant associations between treatment cycles or stage and any of the persistent symptoms. Therefore this model is not presented in a table.

neuropathy complaints among patients treated with (R-)CHOP14 might be that these patients receive vincristine (whereby neuropathy is a known side-effect) in a quicker succession compared to patients treated with (R-)CHOP21.
An explanation for the higher fatigue prevalence among the (R-)CHOP14 group compared to the (R-)CHOP21 group (47% versus 35%) is likely to be the higher toxicity and/or intensity of the (R-)CHOP14 treatment.

Patients who had comorbid diseases, were diagnosed longer ago, or were treated with (R-)CHOP14 more often reported at least one persistent symptom. Subsequently, patients experiencing any of these symptoms/worries reported lower HRQoL compared to patients without these symptoms/worries Therefore, these symptoms should be screened for and alleviated when possible to enhance patients HRQoL.

The current study has some limitations: unfortunately, we did not have HRQoL and symptom scores of patients before treatment. Additionally, we could not compare HRQoL among patients treated in second line (HDCT or/and ASCT) due to small numbers and patients were enrolled in the study at different times since treatment and this time span was significantly different for patients treated with RCHOP14 versus RCHOP21. Although we controlled for time since treatment in the analysis, the variance in time since treatment between the two treatment groups remains an important point of concern. Furthermore, in the present study, neuropathy was only assessed with a single item. To better understand the prevalence and course of neuropathy, research with validated multi-item neuropathy questionnaires and/or nerve conduction tests is necessary. The strengths of our study are that we assessed HRQoL in a population-based setting that includes patients with comorbidities and elderly patients, resulting in a very representative group of DLBCL patients treated in daily practice. In addition, comparison with an age- and sex-matched normative population provides important information about the impact of cancer and its treatment beyond the natural aging process and the impact of comorbidities. Furthermore, we assessed patients twice, which provides important information about the persistence of symptoms over time.

To our knowledge, this is the first study that compared HRQoL outcomes between patients treated with (R-)CHOP14 or (R-)CHOP21. Patients treated with (R-)CHOP14 more often reported tingling in hands and feet, were more often fatigued and had more often a slowed down feeling compared to patients treated with (R-)CHOP21. They furthermore reported a lower global health status/HRQoL. Based on these findings with respect to HRQoL, R-CHOP21 seems the preferred treatment in DLBCL patients. In addition, clinicians should be alert for symptoms that occur among DLBCL patients even long after diagnosis, as these symptoms have a negative influence on their HRQoL.

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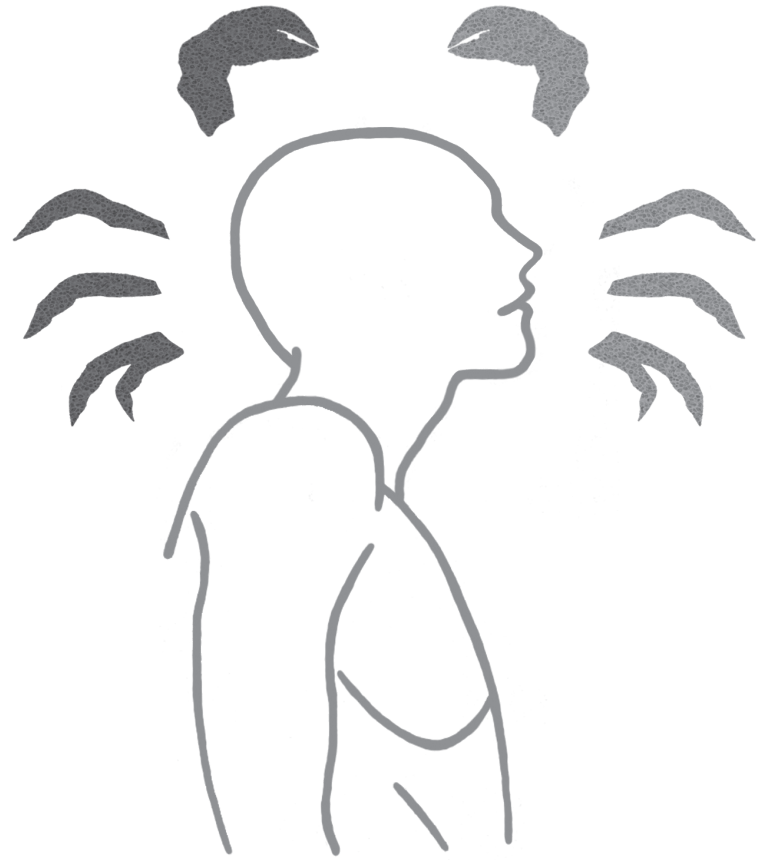
CHAPTER 4

Impact of therapy and disease related symptoms on health-related quality of life in patients with follicular lymphoma: results of the population-based PHAROS-registry



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ABSTRACT

Objectives
The increasing number of longer living patients with follicular lymphoma (FL) and serious side effects of treatment, urged us to study the health-related quality of life (HRQoL) and persistent (treatment-related) symptoms in unselected patients after different treatment modalities and compare HRQoL of patients with a normative population.
Methods
The population-based Eindhoven cancer registry was used to select patients diagnosed with FL during 2004-2010. The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) was completed twice, with a one-year interval. This questionnaire was also completed by a age-and sex-matched normative population (N=580). Detailed data on treatment were extracted from the cancer registry and Population-based HAematological Registry for Observational Studies (PHAROS).
Results
Of the 181 patients who were invited, 148 responded (82%, T1). Patients treated with immunochemotherapy reported clinically relevant higher mean fatigue scores than those who underwent radiotherapy (p=0.02). No differences were observed on the other HRQoL scales between treatment groups. Mean HRQoL scores were worse for FL patients treated with immunochemotherapy compared to a normative population (p<0.01). A quarter to 50% of patients persistently reported to be slowed down, lethargic, or persistently worried about future health or was limited in social activities. Subsequently, patients reporting these symptoms/worries had a lower global health status/HRQoL.
Conclusion
Alertness for persistent symptoms that occur during and after treatment of FL patients is needed and may help to avoid lasting negative influence on their HRQoL.

INTRODUCTION

Follicular lymphoma (FL) is the second most common subtype of non-Hodgkin lymphoma (NHL), and represents 20-25% of all NHL with approximately 17,000 new diagnoses per year in the US and 850 in the Netherlands[1, 2]. Worldwide, it is estimated that there were approximately 770,000 people alive in 2008, up to five years after their NHL diagnosis[3]. FL is often slowly growing and usually responds well to treatment, but is very hard to cure. There are several treatment options: radiotherapy (mostly stage I or early stage II), watchful waiting, or immunochemotherapy[4, 5].

Besides tumor control, the effect of therapy on (long-term) health-related quality of life (HRQoL) is of great importance for the individual patient. Up to now, several studies investigated HRQoL among patients with NHL in general or aggressive lymphoma[6-14], however, research specifically focusing on FL patients is limited. This is important as different types of NHL have different prognosis and treatment modalities, which might affect patients HRQoL in different ways. Three cross-sectional studies investigating HRQoL among FL patients were identified[15-17], whereby HRQoL was only assessed at one time point. Although this important research provides a good overview of the HRQoL of patients on a certain time point, the course of HRQoL and the persistence of symptoms over time remains unknown.

The aims of the present study were to 1) evaluate HRQoL and persistent symptoms/worries among unselected patients with FL after different treatment modalities in comparison with a normative population, 2) assess the prevalence of patients who report persistent symptoms/worries over a one-year time span and assess their impact on global health/HRQoL. We hypothesized that HRQoL in patients would be inferior to a normative population and be lower when they underwent immunochemotherapy compared to patients treated with radiotherapy or patients under watchful waiting. We furthermore hypothesized that patients with persistent symptoms would report a significantly lower global health/HRQoL than patients without these symptoms.

METHODS

Setting and population
This study took place within the scope of the Population-based HAematological Registry for Observational Studies (PHAROS), an extension of the Netherlands Cancer Registry (NCR). The NCR was used to select all patients in an area covering approximately 40% of the Dutch population, who were diagnosed with FL as defined by the International Classification of Diseases for Oncology-3 codes (ICD-O-3) between January 1, 2004 and December 31, 2010[18]. The NCR-data of these patients (including date of diagnosis, morphology, gender, date of birth and stage) were replenished with details on treatment, adverse events and treatment outcomes from PHAROS. Additionally, a longitudinal population-based survey was set up among FL patients registered with the Eindhoven Cancer Registry (ECR) which is part of NCR. The database with patients diagnosed between January 1, 2004 and December 31, 2010 was linked with the database of the Central Bureau for Genealogy to exclude patients who were deceased. HRQoL and symptoms

were collected within PROFILES (Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship). PROFILES is a registry for the study of the physical and psychosocial impact of cancer and its treatment from a dynamic, growing population-based cohort of both short and long-term cancer survivors[19].
In May 2009, patients newly diagnosed between January 2004 and January 2009 were included in the study and received the first questionnaire. In November 2009 and May 2011 patients newly diagnosed after the last inclusion date were subsequently invited to participate (T1) to include all patients diagnosed up to December 31, 2010. Patients received the subsequent questionnaire (T2) one year after T1. Ethical approval for the study was obtained from a certified Medical Ethics Committee (of the Maxima Medical Centre in Veldhoven, The Netherlands; number 0734).

Study measures
The Dutch validated version of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) was used to assess HRQoL[20]. Answer categories range from one (not at all) to four (very much). After linear transformation, all scales and single item measures range in score from 0 to 100. A higher score on function scales and global health and quality of life scale implies a better HRQoL, whereas for symptoms a higher score refers to more symptoms[20].
The Dutch version of the EORTC CLL-16 was used to assess disease and treatment-related specific symptoms and worries. This questionnaire, originally developed for patients with Chronic Lymphocytic Leukemia, was used in the absence of a true non-Hodgkin lymphoma questionnaire. After discussion with specialists treating both CLL and FL patients we decided to administer the questionnaire since most problems are both applicable for CLL and FL patients. Tingling in hands/feet was added to this questionnaire, as it appeared from the literature and from comments of patients on earlier questionnaires. Answer categories range from one (not at all) to four (very much).
Comorbidity at the time of survey was categorized according to the adapted Self-administered Comorbidity Questionnaire (SCQ)[21]. Patients' marital status and educational level were also assessed in the questionnaire. Clinical data was obtained from the NCR and PHAROS.
Patients who received one treatment line or received the same treatment line twice were categorized according to their treatment. For patients who received two or more different treatment lines, the treatment category was based on the sum of treatments before completion of the questionnaire. Patients were categorized in the group of most expected impact on HRQoL: 1: (rituximab), cyclophosphamide, doxorubicin, vincristine, prednisone ((R-)CHOP), 2: (rituximab), cyclophosphamide, vincristine, prednisone ((R-)CVP) or (rituximab), chlorambucil ((R-)chlorambucil),3: Radiotherapy. For example, if patients received (R-)CVP followed by (R-)CHOP before completion of the questionnaire they were classified as (R-)CHOP.

Normative population
The normative population was selected from a reference cohort of 2040 individuals from the general Dutch population (CentER panel)[22]. The set of questionnaires completed by this normative population in November 2011 included the EORTC QLQ-C30, SCQ and data on socio-demographics. This cohort is considered representative for the Dutch-speaking population in

the Netherlands. From this normative population an age- and sex-matched selection was made of 580 persons to compare HRQoL with the FL patients. For matching, ten strata were formed using sex and age (5 categories). Within each stratum a maximum number of persons from the reference cohort were randomly matched according to the strata frequency distribution of the patients. This resulted in 580 matched cancer-free individuals for 148 patients.

Statistical analyses
Differences in socio-demographic and clinical characteristics between respondents and non-respondents (never completed a questionnaire) or patients with unverifiable addresses on T1 were assessed with a chi-square or t-test, where appropriate. Differences in socio-demographic and clinical characteristics between patients who completed one questionnaire or patients who completed two questionnaires on T1 were also assessed with a chi-square or t-test, where appropriate.
The mean EORTC QLQ-C30 scores from the FL patients were compared with an age- and sex-matched Dutch normative population using independent sample t-tests.
Analyses of covariance (ANCOVA) were carried out to compare the mean EORTC QLQ-C30 scores; logistic regression analyses were used to compare the prevalence of EORTC CLL-16 symptoms and tingling in hands/feet between patients treated with different therapies adjusted for age and time since diagnosis. Logistic regression analyses were also used to compare the prevalence of EORTC CLL-16 symptoms per period since treatment. Symptoms/worries were dichotomized as present (answer categories 'a bit', 'quite a bit' or 'very much') or not present (answer category 'not at all').
Analyses of covariance (ANCOVA) were also carried out to compare the mean EORTC QLQ-C30 global health status/HRQoL scale between patients with or without persistent symptoms/worries adjusted for sex, age, number of comorbidities and time since diagnosis. Persistent symptoms were defined as symptoms present at both T1 and T2. Logistic regression analyses were used to evaluate if age, sex, comorbidity and time since diagnosis were associated with persistent symptoms.
Statistical analyses were performed using SAS (version 9.3 for Windows; SAS Institute Inc., Cary, NC). P values of <0.05 were considered statistically significant. The evidence-based guideline for interpretation of the EORTC QLQ-C30 was used to determine clinical relevant differences between groups. This guideline defines a minimum number of points that is required to detect a clinical relevant difference. These differences range for example from at least 3 points for the cognitive functioning scale and at least 5 points for the fatigue scale[23]. Patients were determined to be fatigued with an EORTC QLQ-C30 fatigue score >22.6 (i.e. mean of normative population + minimal required difference of 5 points).

RESULTS

Patients and normative population
One hundred forty eight FL patients completed the first questionnaire (T1, 82% response rate; Figure 1) and subsequently, 92 patients again one year later (T2, 50%). Mean age at T1 was 59 years and 57% were male. Mean time since diagnosis was 2.6 years and 77% of patients

underwent one treatment line. (R-)CVP was received by 35%, (R-)CHOP by 25%, (R-)chlorambucil by 6%, and radiotherapy by 16% of patients. The other patients were under watchful waiting (13%) or received other or no treatment (5%). On T1, 140 patients (95%) were no longer receiving active treatment or maintenance therapy, and on T2 this was 93%. Two-third of patients reported one or more comorbid conditions, the most common being arthritis, back pain and hypertension. Patients who underwent radiotherapy were more often diagnosed with early stage disease compared to patients treated otherwise (Table 1).

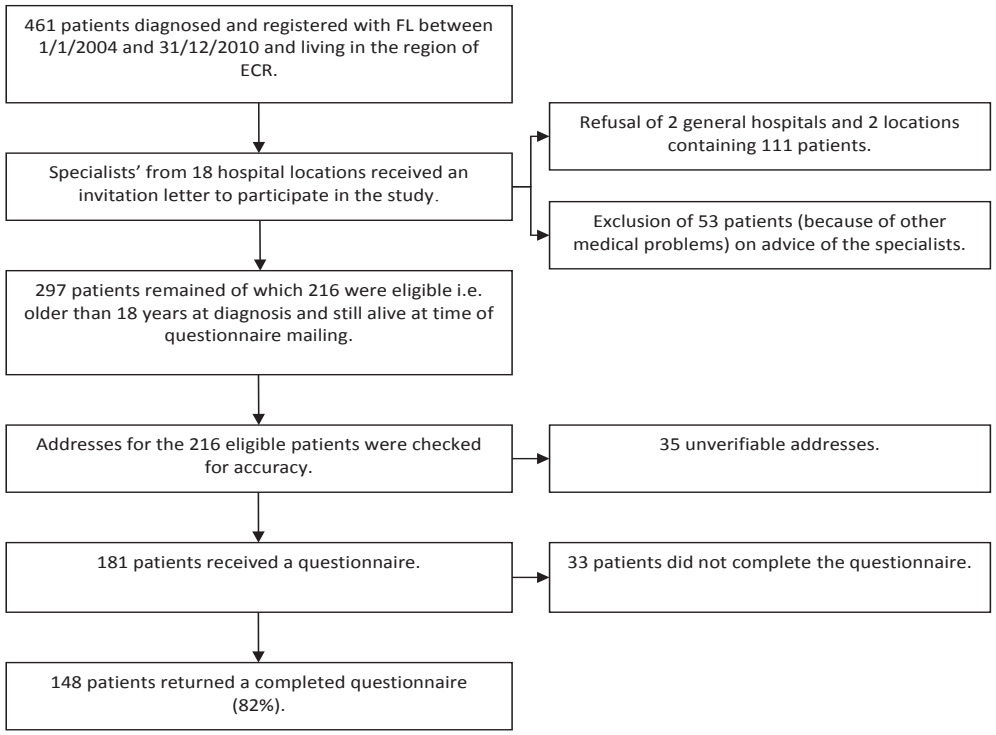
With respect to the age- and sex-matched normative population, mean age was 59 years and 61% were men. Almost two-third (66%) of respondents reported one or more comorbid conditions, the most common were hypertension and back pain.

Quality of data

Non-response analysis

At T1, no statistically significant differences were observed between respondents and non-respondents (N=33) and between respondents and patients with unverifiable addresses (N=35) for sex, age, time since diagnosis/treatment, stage, treatment and number of treatment lines (data not shown).

Figure 1. Flow chart of the data collection process.



Note. FL=Follicular Lymphoma, ECR=Eindhoven Cancer Registry.

Table 1. Socio-demographic and clinical characteristics of respondents according to treatment regime.

	Patients under active surveillance N=19	Patients treated with radio therapy N=23	Patients treated with (R-)CVP/(R-) Chlorambucil N=61	Patients treated with (R-) CHOP N=37	Patients treated with other therapy N=8	
	N (%)	N (%)	N (%)	N (%)	N (%)	p-value
Gender						0.92
Male	11 (58)	12 (52)	37 (61)	22 (59)	3 (38)	
Female	8 (42)	11 (48)	24 (39)	15 (41)	5 (63)	
Age (at time of survey) (mean±SD)	59 (13)	62 (12)	60 (12)	58 (14)	59 (15)	0.52
<45 years	2 (11)	2 (9)	14 (23)	7 (19)	3 (38)	
45-60 years	7 (37)	7 (30)	13 (21)	12 (32)	1 (13)	
61-75 years	8 (42)	11 (48)	23 (38)	14 (38)	2 (25)	
75+ years	2 (11)	3 (13)	11 (18)	4 (11)	2 (25)	
Time since diagnosis (mean±SD)	2.2 (1.1)	2.6 (1.2)	2.6 (1.3)	2.8 (1.3)	3.0 (1.3)	0.95
Time since treatment						0.13
0-1 year since treatment	NA	2 (9)	21 (36)	12 (32)	Missing	
1-2 year since treatment	NA	14 (61)	19 (32)	9 (24)	Missing	
2-3 year since treatment	NA	1 (4)	7 (12)	5 (14)	Missing	
3-5 year since treatment	NA	6 (26)	12 (20)	11 (30)	Missing	
Number of treatment lines						0.15
1st treatment line	19 (100)	19 (86)	43 (70)	26 (70)	6 (86)	
Subsequent treatment line	0 (0)	3 (14)	18 (30)	11 (30)	1 (14)	
Stage at diagnosis						<0.01
I	1 (5)	17 (74)	2 (3)	4 (11)	2 (25)	
II	5 (26)	3 (13)	10 (16)	6 (16)	1 (13)	
III	7 (37)	2 (9)	17 (28)	6 (16)	4 (50)	
IV	6 (32)	1 (4)	32 (52)	21 (57)	1 (13)	
Selfreported comorbidities						0.92
No comorbidities	7 (37)	8 (36)	19 (33)	9 (27)	3 (43)	
1 comorbidity	6 (32)	6 (27)	17 (30)	8 (24)	3 (43)	
2 or more comorbidities	6 (32)	8 (36)	21 (37)	16 (48)	1 (14)	
Marital Status						0.24
Partner	15 (79)	16 (73)	47 (77)	33 (92)	6 (75)	
No partner	4 (21)	6 (27)	14 (23)	3 (8)	2 (25)	
Education level[$]						0.45
Low	4 (22)	5 (24)	5 (8)	3 (8)	0 (0)	
Medium	10 (56)	11 (52)	40 (67)	24 (65)	4 (57)	
High	4 (22)	5 (24)	15 (25)	10 (27)	3 (43)	

Note. (R-)CVP=rituximab, cyclophosphamide, vincristine, prednisone; (R-)CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; (R-)chlorambucil=rituximab, chlorambucil; NA=not applicable; [$]Education levels included low= no/primary school; medium= lower general secondary education/vocational training; or high= pre-university education/ high vocational training/university.

Analysis between patients who completed one or more questionnaires

FL patients who completed two questionnaires had a significantly longer mean time since diagnosis at time of first enrollment than patients who completed only one questionnaire (2.8 versus 2.3 years, p=0.04). Patients who completed two questionnaires also more often had a partner (85% versus 70%, p=0.02). No statistically significant differences were observed between these groups for global health status/QoL score at first questionnaire completion ($\overline{X}$ =74 versus $\overline{X}$ =71, p=0.37) or for sex, age, stage, treatment, comorbidities, and educational level (data not shown).

Comparison HRQoL of FL patients with the normative population

FL patients with a watchful waiting approach reported significantly and clinically relevant higher fatigue mean scores compared to the age- and sex-matched normative population (p=0.02, Figure 2). They also had lower mean scores on other HRQoL scales, although not statistically significant. No statistically significant differences were observed between FL patients who underwent radiotherapy and the normative population. FL patients treated with (R-)CVP/(R-)chlorambucil reported significantly and clinically relevant deteriorated mean scores on all HRQoL scales except for pain and constipation; patients treated with (R-)CHOP reported significantly and clinically relevant deteriorated mean scores on all HRQoL scales except for global health status, pain, appetite loss and diarrhea (Figure 2). Cognitive and social functioning, fatigue, dyspnea and sleeping problems were the most affected HRQoL domains in patients treated with (R-)CVP/(R-)chlorambucil or (R-)CHOP.

HRQoL and symptoms/worries in relation to treatment

Patients treated with (R-)CHOP or (R-)CVP/(R-)chlorambucil reported statistically significant and clinically relevant higher mean fatigue scores compared to patients who underwent radiotherapy (p=0.02; Figure 2). No statistically significant differences were observed on the other HRQoL scales or on the symptoms/worries between the treatment groups (Figure 2 and Table 2). A sub analysis between patients who were under wait and see (n=19), who underwent one active treatment line (n=94)) and patients who underwent 2 or more active treatment lines (n=33) showed no differences on HRQoL (data not shown).

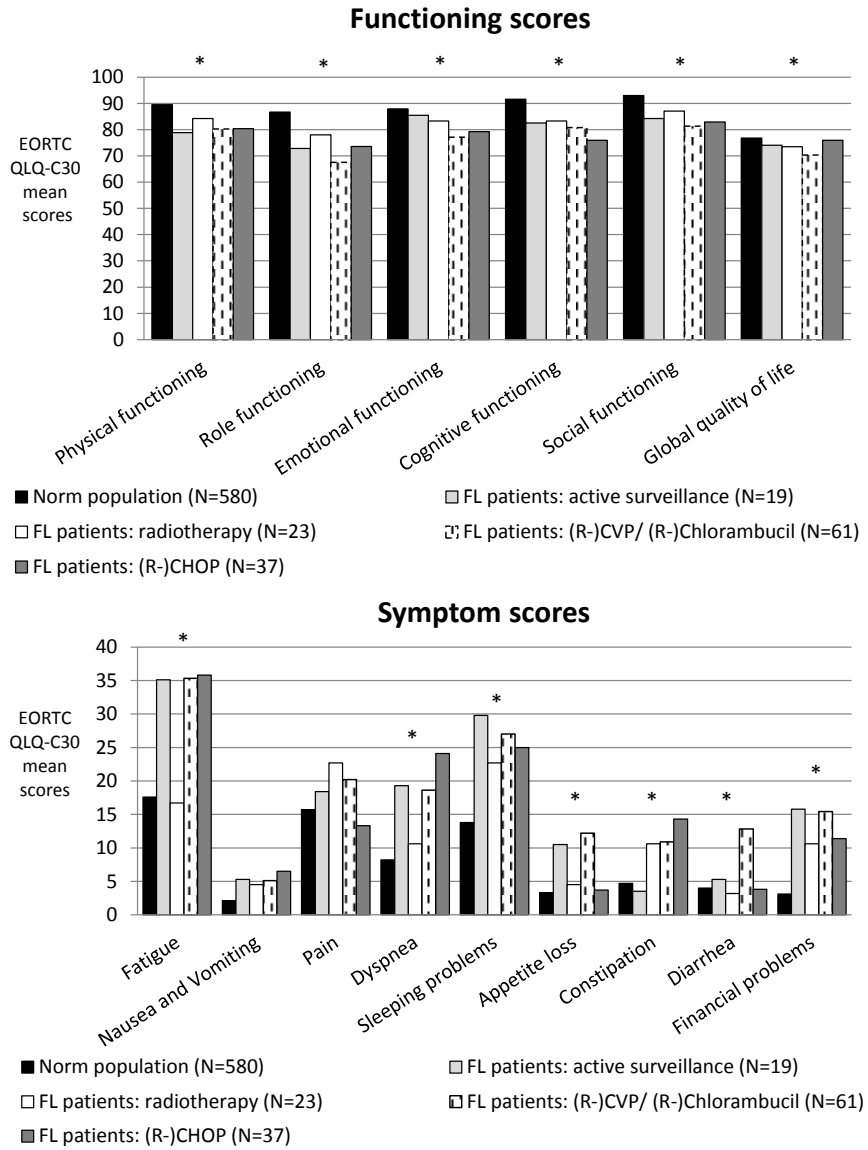
The most frequently reported symptoms/worries (by at least one-third of all patients) on T1 were worry about future health (65%), feeling slowed down (48%), skin problems (46%), night sweats (43%), abdominal discomfort (38%), being limited in social activities (35%), feeling lethargic (35%) and having a dry mouth (33%; Table 3). Although not significantly different, the prevalence of symptoms/worries seemed highest among patients up to one year after treatment (data not shown).

Persistent symptoms/worries and the relation with HRQoL

The most frequently reported persistent symptoms (i.e. symptoms present at T1 and T2) by patients who completed the questionnaire again one year later, were worry about future health (51%), night sweats (35%), feeling slowed down (34%), skin problems (30%), feeling lethargic (25%), abdominal discomfort (24%), being limited in social activities (23%), and having a dry mouth (23%, Table 3). Furthermore, it was observed that that 2-20% of patients reported an improvement of symptoms from T1 to T2 and 8-17% of patients reported a deterioration of symptoms (Table 3).

Patients who reported to be persistently slowed down, lethargic, being limited in social activities or worrying about future health had statistically significantly and clinically relevant lower EORTC global health status/HRQoL compared to patients without these persistent symptoms/worries (Figure 3; all p<0.01). These four symptoms were furthermore more often reported by patients with comorbid conditions. Persistent worry about future health was also reported more often by younger patients. Sex and time since diagnosis were not associated with the presence of persistent symptoms (data not shown).

Figure 2. Differences on EORTC QLQ-C30 mean functioning, global quality of life and symptom scores between FL patients according to treatment schedule and an age- and sex-matched normative population (N=580).



Note. *p<0.05 for: FL patients treated with (R-)CHOP compared to the normative population for physical, role, emotional, cognitive and social functioning. FL patients treated with (R-)CVP/(R-)Chlorambucil compared to the normative population for physical, role, emotional, cognitive and social functioning and global quality of life.
Note. *p<0.05 for: FL patients under active surveillance compared to the normative population for fatigue. FL patients treated with (R-)CHOP compared to the normative population for fatigue, dyspnea, insomnia, constipation and financial problems. FL patients treated with (R-)CVP/(R-)Chlorambucil compared to the normative population for fatigue, dyspnea, insomnia, appetite loss, constipation, diarrhoea and financial problems. FL patients treated with (R-)CVP/(R-)Chlorambucil or (R-)CHOP compared to FL patients treated with radiotherapy.

Table 2. Differences between FL patients under active surveillance, treated with radiotherapy, (R-)CVP/(R-)Chlorambucil or (R-)CHOP on EORTC CLL-16 symptoms and worries.

	Patients under active surveillance	Patients treated with radio-therapy	Patients treated with (R-)CVP/(R-)Chlorambucil	Patients treated with (R-)CHOP	
EORTC CLL-16	**N=19**	**N=23**	**N=61**	**N=37**	p-value*
Weight loss	3 (16)	4 (18)	14 (23)	6 (16)	0.54
Dry mouth	6 (32)	6 (27)	22 (37)	13 (35)	0.79
Bruises	3 (17)	2 (9)	5 (8)	1 (3)	0.33
Abdominal discomfort	5 (26)	6 (27)	23 (38)	21 (57)	0.05
Temperature up/down	11 (58)	2 (9)	7 (12)	7 (19)	0.27
Night sweats	7 (37)	6 (27)	27 (45)	17 (46)	0.82
Skin problems	8 (42)	8 (38)	31 (52)	18 (49)	0.74
Feeling ill or unwell	6 (32)	4 (19)	17 (28)	4 (11)	0.08
Feeling lethargic	8 (42)	5 (24)	28 (47)	11 (30)	0.18
Feeling slowed down	6 (32)	6 (29)	36 (60)	18 (49)	0.22
Limited in activities	6 (32)	5 (23)	23 (39)	16 (43)	0.52
Worried future health	14 (74)	11 (50)	40 (66)	27 (73)	0.48
Chest infections	4 (22)	3 (14)	14 (24)	7 (19)	0.86
Other infections	3 (17)	2 (9)	10 (17)	4 (11)	0.53
Repeated antibiotics	2 (11)	3 (14)	10 (17)	5 (14)	0.98
Worried about infections	5 (28)	3 (14)	13 (22)	13 (35)	0.08
Tingling hands/feet	4 (21)	4 (18)	18 (30)	8 (22)	0.72

Note. FL=Follicular Lymphoma; (R-)CVP=rituximab, cyclophosphamide, vincristine, prednisone; (R-)CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; (R-)Chlorambucil=rituximab, chlorambucil; EORTC CLL-16=European Organisation for Research and Treatment of Cancer Chronic Lymphocytic Leukemia-16 questionnaire.
*p-value adjusted for age and time since diagnosis.

DISCUSSION

HRQoL was lower among FL patients treated with (R-)CHOP or (R-)CVP/(R-)chlorambucil compared to a normative population, which confirms what we expected. Patients under active surveillance or those who underwent radiotherapy reported similar HRQoL compared to the normative population, except for fatigue. Patients treated with (R-)CHOP or (R-)CVP/(R-)chlorambucil reported fatigue more often compared to patients treated with radiotherapy. A quarter to 50% of patients reported persistent symptoms/worries which also affected their EORTC global health status/HRQoL negatively. About one third of patients reported fluctuating symptoms, of which 2-20% reported an improvement and 8-17% deterioration.

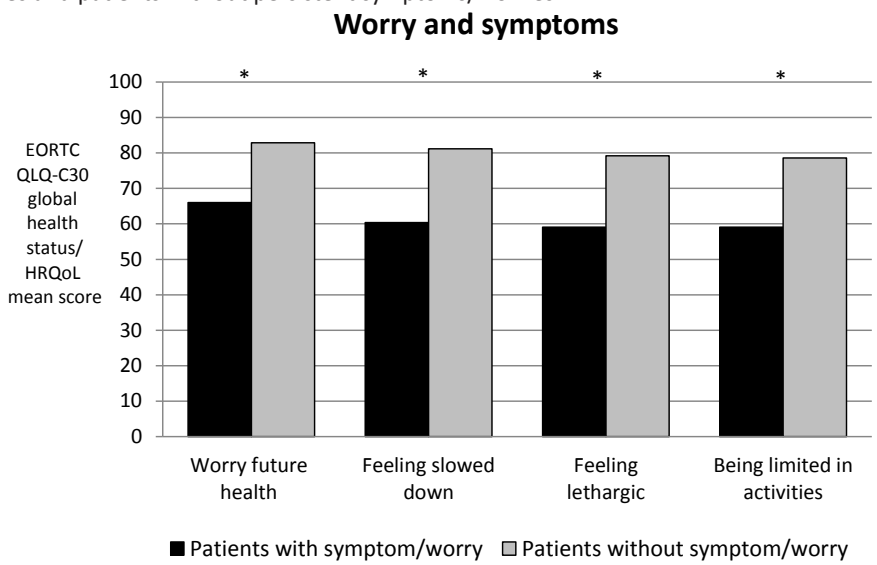
Among 124 German patients a lower HRQoL was also observed between FL patients and a normative healthy population[15]. Studies comparing HRQoL between lymphoma patients in general and a normative population[11, 13, 24, 25] also observed lower HRQoL among patients.

Table 3. Number and percentage of FL patients who reported EORTC CLL-16 symptoms/worries on T1 (N=148) and who reported persistent symptoms on both T1 and T2 (N=92) (all treatment categories combined).

EORTC CLL-16	Symptoms/ worries on T1 N=148		Persistent symptoms/ worries on both T1 and T2 N=92		Improvement in symptoms from T1-T2 N=92		Deterioration in symptoms from T1-T2 N=92	
	N	%	N	%	N	%	N	%
Weight loss	28	19%	3	3%	11	12%	7	8%
Dry mouth	48	33%	21	23%	8	9%	11	12%
Bruises	12	8%	2	2%	2	2%	8	9%
Abdominal discomfort	56	38%	22	24%	11	12%	8	9%
Temperature up/down	21	14%	5	5%	9	10%	4	4%
Night sweats	63	43%	32	35%	8	9%	14	15%
Skin problems	67	46%	28	30%	18	20%	12	13%
Feeling ill or unwell	33	23%	11	12%	10	11%	9	10%
Feeling lethargic	51	35%	23	25%	10	11%	12	13%
Feeling slowed down	69	48%	31	34%	14	15%	13	14%
Tingling hands/feet	36	25%	15	16%	10	11%	16	17%
Limited in activities	51	35%	21	23%	11	12%	10	11%
Worried future health	96	65%	47	51%	10	11%	15	16%
Chest infections	29	20%	8	9%	7	8%	13	14%
Other infections	19	13%	8	9%	5	5%	6	7%
Repeated antibiotics	20	14%	5	5%	8	9%	10	11%
Worried about infections	35	24%	11	12%	13	14%	9	10%

Note. FL=Follicular Lymphoma; EORTC CLL-16= European Organisation for Research and Treatment of Cancer Chronic Lymphocytic Leukemia-16 questionnaire; T1=first measurement, T2=second measurement after one year. Symptoms/worries were dichotomized as present (answer categories 'a bit', 'quite a bit' or 'very much') or not present (answer category 'not at all'). Persistent symptoms were defined as symptoms present at both T1 and T2.

Figure 3. EORTC QLQ-C30 global health status/HRQoL scores of patients with persistent symptoms/ worries and patients without persistent symptoms/worries.



Note. EORTC QLQ-C30= European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30. Symptoms/worries were dichotomized as present (answer categories 'a bit', 'quite a bit' or 'very much') or not present (answer category 'not at all'). Persistent symptoms were defined as symptoms present at both T1 and T2.
*P-value <0.01; adjusted for sex, age, number of comorbidities and time since diagnosis

Two studies also compared HRQoL between treatment regimes, although the majority of the included patients received several treatment lines compared to 77% with one treatment line in our study. FL patients who received high-dose chemotherapy and autologous stem cell transplant reported better HRQoL on two domains, i.e. social functioning and pain compared with patients after R-CHOP[15]. An American study among 137 FL patients observed that after frontline therapy no difference in HRQoL was observed between patients treated with rituximab maintenance therapy versus patients under active surveillance[26]. Our observation that FL patients who underwent immunochemotherapy reported fatigue more often compared to patients after radiotherapy can also result from the extensiveness of the disease, although there was no/little difference in HRQoL between patients who underwent one or more treatment line.

We observed no significant differences in the prevalence of symptoms/worries with respect to time since treatment. This is in line with a study among 761 NHL survivors focusing on HRQoL[13]. A study among 459 Hodgkin lymphoma patients even observed that patients 7-10 years after diagnosis reported higher anxiety and depression scores compared to patients 3-6 years after diagnosis[27]. So, while lymphoma survivors may be expected to return to normal life soon after treatment ends, there is growing evidence that they continue to be burdened by the physical and psychosocial effects of the cancer and related treatment.

FL patients who persistently reported to be slowed down or even lethargic scored on average 20 points lower on global health status/HRQoL than patients without these complaints. Fatigue is a common problem among a variety of cancer patients[28-30] as also among lymphoma patients[31] and it is associated with decreased HRQoL[32], high levels of psychological distress[33, 34] and has an effect on patient's daily life. Healthcare providers should be encouraged to inquire about the presence of this symptom as fatigued patients may benefit from pharmacologic and/or non-pharmacologic treatments, such as cognitive-behavioral interventions and exercise[35].

The current study has some limitations: although the response rate at T1 was high (82%), the response on T2 was much lower. Patients who completed two questionnaires were more often diagnosed longer ago. This could imply survivorship bias, i.e. only patients who survived could participate a year later. Furthermore, the sample size of some treatment categories was small, which made it more difficult to draw conclusions on HRQoL with respect to variation in treatment. For example, FL patients under active surveillance did not report statistically significant different mean scores compared to the normative population. Although, the mean scores were substantially lower for physical, role, cognitive and social functioning and higher for insomnia and p-values were between 0.06 and 0.09. This might be a result of the small sample size, therefore, research with larger samples is recommended to study if FL patients under active surveillance in fact report a deteriorated HRQoL.

The strengths of our study are that we assessed HRQoL in a population-based setting that includes patients with comorbidities and elderly patients, resulting in a very representative group of FL patients treated in daily practice. In addition, comparison with an age- and sex-matched normative population provides important information about the impact of cancer beyond the natural aging process and the impact of comorbidities. Furthermore, we assessed patients at two time points, which provides important information about the persistence of symptoms over time.

In conclusion, up to five years after diagnosis FL patients treated with (R-)CHOP or (R-)CVP/(R-) chlorambucil still report a substantially lower HRQoL compared to an age- and sex-matched normative population. Furthermore, a quarter to 50% of patients persistently reported to be slowed down, lethargic, or persistently worried about future health or was limited in social activities. Subsequently, patients reporting these symptoms/worries had a lower global health status/HRQoL. Alertness for persistent symptoms that occur during and after treatment of FL patients is needed and may help to avoid lasting negative influence on their HRQoL.

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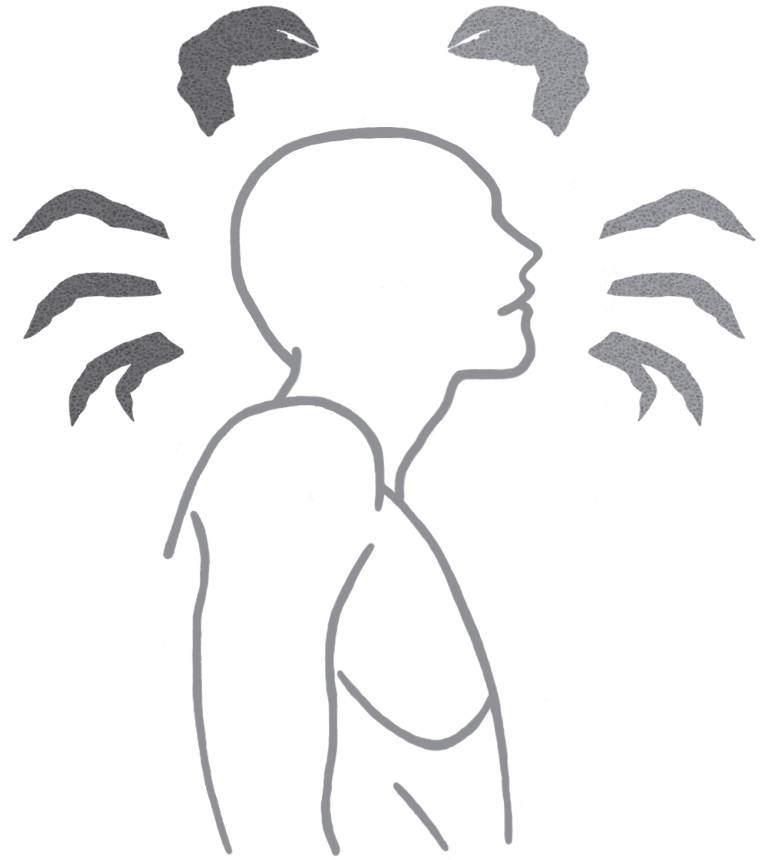
CHAPTER 5

Impact of active surveillance, chlorambucil and other therapy on health-related quality of life in patients with CLL/SLL in the Netherlands



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ABSTRACT

As survival of patients with Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma (CLL/SLL) increases and the number of patients who live long rises, health-related quality of life (HRQoL) becomes a relevant endpoint. Few studies investigated this, mainly as a secondary endpoint in randomized clinical trials where patients with early stage CLL/SLL, and elderly/frail patients were underrepresented. The aim of our study was to assess HRQoL in a population-based setting, including these previously underrepresented patients.

Out of 175 patients diagnosed with CLL/SLL between 2004 and 2011, 136 (78%) returned the HRQoL-questionnaire. The outcomes were compared to an age- and sex-matched norm population. Detailed data on stage and treatment were extracted from a population-based hematological registry (PHAROS).

Patients ever treated for CLL/SLL reported significantly poorer HRQoL than the norm population ($p<0.01$) with large clinically important differences. Interestingly, no differences were observed between the norm population and patients under active surveillance. In contrast to our hypothesis, patients treated with chlorambucil reported the lowest HRQoL scores.

Drastic, long-lasting negative effects of starting treatment on HRQoL can not be excluded, whereas active surveillance does not seem to provoke worrying, anxiety, or depressive symptoms. Therefore, it seems wise to conduct elaborate research into the impact of starting therapy on HRQoL, especially in patients that are underrepresented in most clinical trials, and thoroughly consider its results during revision of treatment guidelines.

INTRODUCTION

Chronic Lymphocytic Leukemia (CLL) is the most common type of leukemia in adults in western countries, both in terms of incidence and prevalence, with more than 700 diagnoses per year in the Netherlands. The incidence in Europe is 4.9 per 100,000 person years[1]. Small Lymphocytic Lymphoma (SLL) is an indolent form of non-Hodgkin Lymphoma with morphological and immunophenotypic features similar to CLL. Hence, the most recent World Health Organization (WHO) classification scheme for hematopoietic malignancies considers CLL and SLL to be different manifestations of the same disease and combines these entities into one disease category; CLL/SLL[2]. Median survival time is 10 years, ranging from months when the disease behaves aggressively, to decades for patients with an indolent course of the disease[3]. Approximately 70% of the patients is older than 65 years at the time of diagnosis[4].

Active surveillance remains standard practice for patients with asymptomatic, early stage CLL/SLL, as randomized clinical trials (RCTs) failed to show a statistically significant difference in survival between early versus deferred therapy[5]. For young and more or less fit patients with advanced disease, fludarabine, cyclophosphamide, and rituximab (FCR) became standard first line treatment, after a phase III study showed improvement of survival after addition of a monoclonal antibody in 2010[6]. During the study period, chlorambucil was the first choice for elderly and/or frail patients, as up until recently, no RCTs with this group of patients showed improved therapeutic results over chlorambucil[7, 8]. In 2014, the results of the CLL11-trial were published, which showed that combining an anti-CD20 antibody with chemotherapy improves outcomes in patients with CLL and coexisting conditions[9].

Since the number of CLL/SLL patients who live long after their diagnosis is rising (due to improvement of response to treatment and survival rates), health-related quality of life (HRQoL) is a relevant endpoint. Up to now, few studies have investigated HRQoL in CLL/SLL patients[10-12], most as part of randomized clinical trials[13], underrepresenting patients with early stage CLL/SLL, elderly patients and patients with comorbidities.

The aim of the present study was therefore to assess HRQoL in a population-based setting that includes these previously underrepresented patients. We evaluated HRQoL among patients on and off treatment with different treatment modalities and subsequently compared this with an age-and sex-matched norm population to assess the effect of CLL. We hypothesize that patients who received chlorambucil report better HRQoL than patients receiving other chemo-/immunotherapy, as chlorambucil is associated with less toxicity then most other regimens[14]. We expect patients in the active surveillance group to report better HRQoL than patients that were treated, as patients who are under active surveillance may suffer from symptoms from the disease but not from symptoms or side effects of active treatment. Furthermore, we expect that patients who were undergoing treatment during survey completion to report a worse HRQoL than patients who were off treatment, as they experience more effect of the disease on their daily life during treatment. Finally, we expected that active surveillance without treatment

provokes feelings of uncertainty; leading to worrying, anxiety and depressive symptoms as this was observed in men with prostate cancer under active surveillance[15].

PATIENTS AND METHODS

Setting and population

This study took place within the scope of the Population-based HAematological Registry for Observational Studies (PHAROS; www.pharosregistry.nl). PHAROS is a supplement to the Netherlands Cancer Registry (NCR), which is maintained and hosted by Comprehensive Cancer Centre South (CCCS) and Comprehensive Cancer Centre the Netherlands (CCCNL). The NCR was used to select all patients in an area covering approximately 40% of the Dutch population, who were diagnosed with CLL or SLL as defined by the International Classification of Diseases for Oncology-3 codes (ICD-O-3)[16] between January 1st, 2004 and January 1st, 2011. The NCR-data of these patients were replenished with details on stage, (response to) treatment and adverse events.

Additionally, a dynamic longitudinal population-based survey was set up among CLL/SLL patients registered with the Eindhoven Cancer Registry (ECR) of the CCCS, which is a component of NCR. Patients diagnosed between January 1st, 2004 and January 1st, 2011 were linked with the database of the Central Bureau for Genealogy, which collects data on all deceased Dutch citizens through the civil municipal registries, to exclude patients who had deceased. In this survey, patient reported outcomes were collected within PROFILES (Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship). PROFILES is a registry for the study of the physical and psychosocial impact of cancer and its treatment from a dynamic, growing population-based cohort of both short and long-term cancer survivors. PROFILES contains a large web-based component and is linked directly to clinical data from ECR. Details of the data collection method are previously described[17]. Data from the PROFILES registry are available for non-commercial scientific research, subject to study question, privacy and confidentiality restrictions, and registration (www.profilesregistry.nl).

Ethical approval for the study was obtained from a certified Medical Ethics Committee (of the Maxima Medical Centre in Veldhoven, The Netherlands; number 0734).

Study measures

General information was available from the NCR that routinely collects data on tumor characteristics, including date of diagnosis and morphology, and patient's background characteristics, including gender and date of birth. Detailed clinical information was available from the PHAROS-registry that collects additional data including stage and treatment.

We divided patients in treatment categories with hypothesized impact on HRQoL, from most to least: 1) 'R-CHOP', 'FC(R)', '(R-)CVP / Rituximab (+/- chlorambucil) / fludarabine monotherapy', (indicated as 'other chemo- and/or immunotherapy') 2) 'chlorambucil', 3) 'Radiotherapy', 4) 'Active surveillance', and 5) 'No treatment' (e.g. patients who fulfill treatment criteria but refuse therapy). Patients were considered off treatment if the most recent therapy was administered more than three months prior to the date of filling in the questionnaire. Otherwise, patients were considered on treatment.

The Dutch validated version of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) was used to assess HRQoL[18]. Answer categories range from one (not at all) to four (very much). After linear transformation, all scales and single item measures range in score from 0 to 100. A higher score on function scales and global health and quality of life scale implies a better HRQoL, whereas for symptoms a higher score refers to more symptoms[18].

Anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS). In this questionnaire, anxiety and depressive symptoms are measured in two separate subscales of seven items each. Answers range from 0 to 3, and a score ≥8 on either subscale indicates a substantial level of anxiety or depressive symptoms[19, 20].

Worry was assessed with the items 'Worry about future', 'Worry about health', 'Worry about cancer coming back' and 'Worry when new symptoms occur' of the Impact of Cancer Scale (IOC). This measure presents statements to which respondents indicate their level of agreement from 1 (strongly disagree) to 5 (strongly agree)[21, 22].

Co-morbidity at the time of survey was categorized according to the Self-Administered Comorbidity Questionnaire (SCQ). Survivors' marital status and educational level were also assessed in the questionnaire.

Data collection

Patients were included on three time points: May 2009 (patients diagnosed between January 1999 and May 2008); November 2009 (patients diagnosed between May 2008 and May 2009) and May 2011 (patients diagnosed between May 2009 and December 2010).

In order to compare outcomes with those from a normative population we also collected the EORTC QLQ-C30, SCQ[23], marital status and educational level data among 1352 persons without cancer[24]. From this normative population an age- and sex-matched selection was made of 209 persons to compare HRQoL with the CLL patients. For matching, ten strata were formed using sex and age (5 categories). Within each stratum, a maximum number of persons from the reference cohort were randomly matched according to the strata frequency distribution of the patients. This resulted in 209 matched cancer-free individuals for 136 patients.

Statistical analyses

All statistical analyses were performed using SAS (version 9.3 for Windows; SAS Institute Inc., Cary, NC). P values of <0.05 were considered statistically significant. Clinically relevant differences were determined using the evidence-based guidelines for interpretation of the EORTC QLQ-C30 between groups[25].

Patients were determined to be fatigued with an EORTC QLQ-C30 fatigue score >21.9 (mean normative population + small clinically important difference, i.e. 5 points) and low physical functioning was defined as an EORTC QLQ-C30 score <83.2 (mean normative population - small clinically important difference, i.e. 5 points). Patients were considered having anxious symptoms with a HADS anxiety score >8 and having depressive symptoms with a HADS depression score >8[20]. Worry about health and worry about future were considered positive if patients (strongly) agreed with this item.

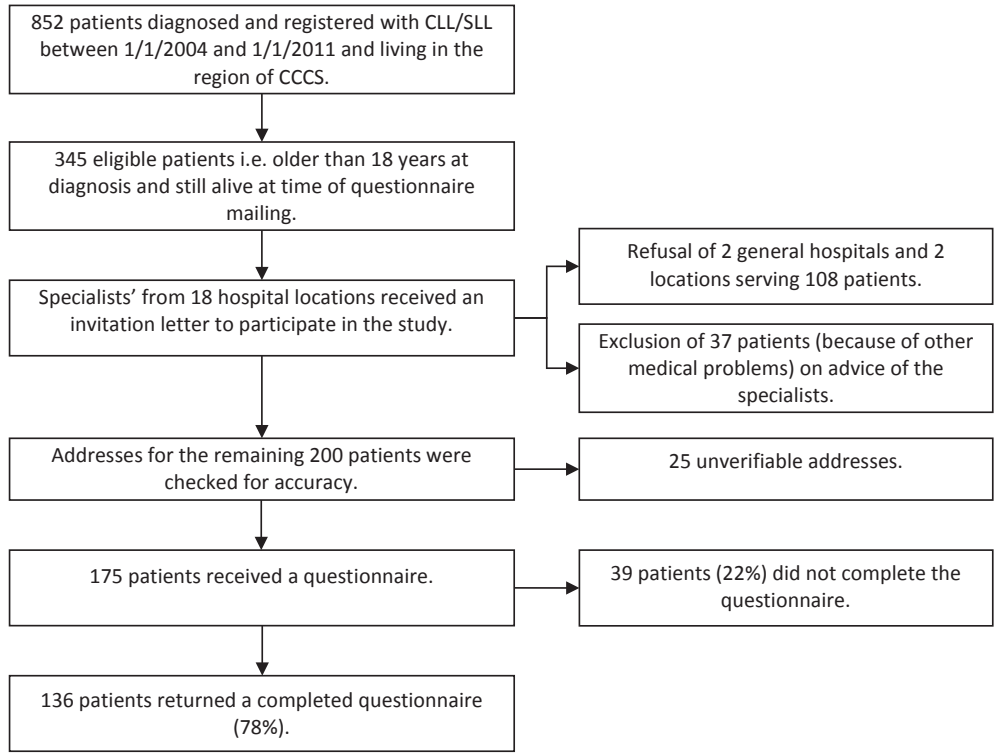
Differences in demographic and clinical characteristics between respondents, non-respondents, and patients with unverifiable addresses and between treatment groups were compared with chi-square analyses and Fisher exact with Montecarlo estimate tests.
Differences in mean EORTC QLQ-C30 scores between CLL/SLL survivors under active surveillance and CLL/SLL survivors treated with chemo- and/or immunotherapy versus an age- and sex-matched Dutch normative population were compared with analysis of variance (ANOVA).
Analysis of covariance (ANCOVA) was carried out to investigate the differences in mean EORTC QLQ-C30, HADS and IOC Worry scores between treatment groups and between on and off treatment after adjustment for sex, age and comorbidity.
Logistic regression models using the dichotomized EORTC QLQ-C30 physical functioning and fatigue scores, HADS anxiety and depression scores and IOC Worry items as outcomes, were conducted to identify variables associated with these outcomes. These were the outcomes that were mentioned to be affected most often in both focus groups and previous studies[26, 27]. Variables were a priori determined, including gender, age, number of comorbidities, time since diagnosis and treatment.

RESULTS

Patients' characteristics

We analyzed data of 200 CLL/SLL patients of whom 175 received a questionnaire that was returned by 136 (78% response rate). Despite the population-based nature of the study, not all eligible patients received a questionnaire. One hundred eight patients did not receive a questionnaire as they were treated in hospitals that did not participate in the survey. We did not expect this to affect the representativeness. Another 37 patients did not receive a questionnaire because their specialist indicated they had other severe medical problems. This could have resulted in a slightly better HRQoL-outcomes (Figure 1).
Non-respondents were significantly older than respondents and patients with unverifiable addresses (mean age at diagnosis 67.7 years versus 63.1 and 61.5 years, respectively). Non-respondents were more often under active surveillance and diagnosed with an early stage, however those differences were not statistically significant. Almost half of the respondents (47%) were diagnosed less than two years prior to survey completion, and active surveillance was the most frequent treatment strategy (49%). Thirty-nine percent of the responding patients were diagnosed with Rai-stage 0. Slightly more than half of the respondents (53%) were younger than 65 years. Seventy-one percent of the patients reported one or more comorbid conditions, the most common were high blood pressure (27%), anemia (22%) and back pain (22%; Table 1).
As expected, patients under active surveillance had more often been diagnosed at an early stage than patients who had received chemo- and/or immunotherapy. Although the patients in the chlorambucil were older than the patients in the other groups (55% being older than 65 years versus 46% in the active surveillance group and 44% in the other chemo-group), and patients under active surveillance were more often males (70% versus 63% and 57% in the chlorambucil-group and other chemo-group respectively), none of the differences other than stage were statistically significant (Table 2).

Figure 1. Flow chart of the data collection process.



Note. CLL/SLL= Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, CCCS= Comprehensive Cancer Center South.

Comparison CLL/SLL patients with age- and sex-matched normative population

CLL/SLL patients treated with chemo- and/or immunotherapy had statistically significantly worse scores on all HRQoL scales (all $p < 0.001$) except for pain, constipation and diarrhea, compared to an age- and sex-matched normative population. A medium clinically important difference was observed for social functioning, fatigue, dyspnea, sleeping problems and financial problems. Other scores represented small clinically important differences. Differences between CLL/SLL survivors under active surveillance and the normative population were not statistically or clinically significant (Figure 2).

Comparison between treatment groups

Compared to patients under active surveillance, patients having received any type of chemo- and/or immunotherapy reported worse scores on physical and role functioning and had more financial problems. Patients treated with chlorambucil also reported worse scores on social functioning and dyspnea compared to patients under active surveillance. The prevalence of fatigue among the chlorambucil group (81%) was almost twice as high compared to the active surveillance group (42%) ($p<0.01$), and also higher than those treated with other chemo-/

Table 1. Socio-demographic and clinical characteristics of questionnaire respondents, non-respondents, and patients with unverifiable addresses.

	Respondents N=136	Non-Respondents N=39	Patients with unverifiable addresses N=25	
	N (%)	N (%)	N (%)	p-value
Gender				0.60
Male	90 (67)	26 (67)	14 (56)	
Female	46 (33)	13 (33)	11 (44)	
Age: mean (SD)	63.1 (10.5)	67.7 (11.0)	61.5 (14.1)	<0.05
<55 years	31 (23)	6 (15)	7 (28)	
55-64 year	41 (30)	4 (10)	7 (28)	
65-74 year	46 (34)	17 (44)	7 (28)	
75+ years	18 (13)	12 (31)	4 (16)	
Treatment				0.19
R-CHOP	4 (3)	0 (0)	1 (4)	
FC(R) / Fludarabine	10 (7)	2 (5)	1 (4)	
(R-)CVP/ Rituximab	16 (12)	4 (10)	2 (8)	
Chlorambucil	27 (20)	1 (3)	7 (28)	
Radiotherapy	3 (2)	2 (5)	1 (4)	
Active surveillance	68 (51)	26 (67)	12 (48)	
None	8 (6)	4 (10)	1 (4)	
Years since diagnosis: mean (SD)	2.7 (1.3)	2.6 (1.4)	2.9 (1.4)	0.36
<2 year	65 (48)	16 (41)	9 (36)	
2-3 years	28 (21)	9 (23)	3 (12)	
>3 years	43 (32)	14 (36)	13 (52)	
Stage at diagnosis				0.87
Rai 0	53 (39)	21 (54)	11 (44)	
Rai 1	25 (18)	6 (15)	6 (24)	
Rai 2	16 (12)	4 (10)	3 (12)	
Rai 3	4 (3)	0 (0)	0 (0)	
Rai 4	7 (5)	0 (0)	0 (0)	
Not Applicable (SLL)	31 (23)	8 (21)	5 (20)	
Number of self reported comorbidities				
0	28 (21)			
1	31 (23)			
>2	66 (48)			
Unknown	11 (8)			
Marital Status				
Partner	105 (77)			
Divorced	11 (8)			
Widowed	13 (9)			
Alone	4 (2)			
Education[$]				
High	28 (20)			
Middle	71 (51)			
Low	34 (25)			

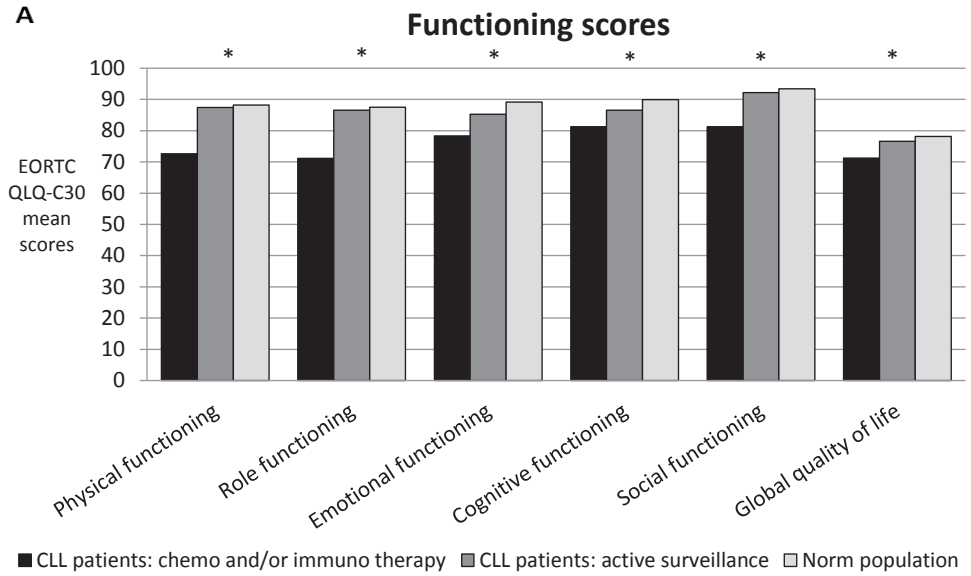
Note: SLL= Small Lymphocytic Lymphoma; [$]Education levels included low= no/primary school; medium= lower general secondary education/vocational training; or high= pre-university education/ high vocational training/university.

Table 2. Socio-demographic and clinical characteristics of respondents according to treatment regime.

	Patients under active surveillance N=68	Patients receiving Chlorambucil N=27	Patients receiving other chemo N=30	
	N (%)	N (%)	N (%)	p-value
Gender				0.4
Male	48 (70)	17 (63)	17 (57)	
Female	20 (30)	10 (37)	13 (43)	
Age: mean (SD)	64.9 (10.8)	68.8 (9.8)	64.2 (2.5)	0.6
<55 years	14 (21)	4 (15)	9 (30)	
55-65 year	23 (34)	8 (30)	8 (27)	
65-75 year	23 (34)	9 (33)	11 (37)	
75+ years	8 (12)	6 (22)	2 (7)	
Time since diagnosis: mean (SD)	2.3 (1.3)	2.9 (1.4)	2.5 (0.9)	0.1
<2 year	40 (59)	8 (30)	15 (50)	
2-3 years	12 (18)	7 (26)	8 (27)	
>3 years	16 (24)	12 (44)	7 (23)	
Treatment phase				0.6
On treatment	NA	8 (30)	7 (23)	
Off treatment	NA	19 (70)	22 (73)	
Stage at diagnosis				<0.0001
Rai 0	38 (56)	5 (19)	6 (20)	
Rai 1	17 (25)	5 (19)	3 (10)	
Rai 2	5 (7)	7 (26)	4 (13)	
Rai 3	0 (0)	3 (11)	1 (3)	
Rai 4	0 (0)	3 (11)	3 (10)	
Not Applicable (SLL)	8 (12)	4 (15)	13 (43)	
Self reported comorbidities				0.9
No comorbidities	15 (25)	4 (16)	8 (28)	
1 comorbidity	18 (30)	9 (36)	9 (31)	
2 or more comorbidities	28 (46)	12 (48)	13 (41)	
Marital Status				0.1
Partner	55 (82)	17 (65)	23 (77)	
Divorced	5 (7)	4 (15)	2 (7)	
Widowed	6 (9)	5 (19)	2 (7)	
Alone	1 (1)	0 (0)	3 (10)	
Education level[$]				0.7
High	14 (21)	6 (23)	4 (13)	
Medium	34 (52)	13 (50)	20 (67)	
Low	18 (27)	7 (27)	6 (20)	

Note: NA= Not Applicable; SLL= Small Lymphocytic Lymphoma; [$]Education levels included low= no/primary school; medium= lower general secondary education/vocational training; or high= pre-university education/ high vocational training/university.

Figure 2A and 2B. Differences on EORTC QLQ-C30 mean functioning and global quality of life scores (A) and symptom scores (B) of CLL/SLL patients treated with chemo and/or immunotherapy (N=57) and CLL/SLL patients under active surveillance (N=68) compared to an age- and sex-matched normative population (N=290).



Note: A higher score on functioning scores implies a better health-related quality of life, whereas a higher score on symptom scores refers to more symptoms. EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; CLL= Chronic Lymphocytic Leukemia; SLL= Small Lymphocytic Lymphoma.
*p<0.01 and clinically important difference between CLL/SLL patients treated with chemo and/or immunotherapy compared to the normative population; Differences between CLL/SLL patients under active surveillance and the normative population were not statistically or clinically significant.

immunotherapy (63%), although not statistically significant. Similarly, patients treated with chlorambucil were also more worried about the future, their health, the cancer coming back and the occurrence of new symptoms than patients in the active surveillance group or patients treated with other chemo-/immunotherapy; although the latter did not reach statistical significance. No difference was observed for anxiety and depressive symptoms between any of the treatment groups (Table 3).

Comparison patients on and off treatment

Compared to an age- and sex-matched normative population, CLL/SLL patients receiving treatment at survey completion scored worse on physical and social functioning, global quality of life, fatigue and sleeping problems with large clinically important differences. Medium clinically important differences were reported for role functioning and pain. For emotional and cognitive functioning the differences between CLL/SLL patients on treatment and the normative population were considered small clinically important.

CLL/SLL patients who no longer received treatment at survey completion scored worse on dyspnea, sleeping problems and financial problems (medium clinically important differences). For physical-, role-, emotional-, and social functioning, fatigue and appetite loss the differences between CLL/SLL patients off treatment and the normative population were considered of small clinically importance. A significantly and large clinically important difference on cognitive functioning was observed between patients still on treatment and patients off treatment ($p<0.01$, Figure 3).

Socio-demographic, disease and treatment variables associated with HRQoL and worry

Multivariate logistic regression analysis showed that low EORTC physical functioning score was positively associated with co-morbidity and treatment. High fatigue scores and health worries were both positively associated with having two or more comorbidities and treatment with chlorambucil. Worrying about the future was negatively associated with age and positively associated with treatment with chlorambucil. No statistically significant associations were observed between HADS anxiety and depressive symptoms and socio-demographic, disease and treatment characteristics (Table 4).

DISCUSSION

In contrast to our hypothesis, patients treated with chlorambucil reported poorest HRQoL. Being treated for CLL/SLL was associated with deteriorated HRQoL longer after treatment than we anticipated, as both patients on and off treatment scored worse on fatigue, sleeping problems and all functional scales (except cognitive functioning) compared to the norm population. We expected patients in the active surveillance group to worry most, but patients treated with chlorambucil worried significantly more. No significant differences in reported anxiety or depressive symptoms between the treatment groups were found.

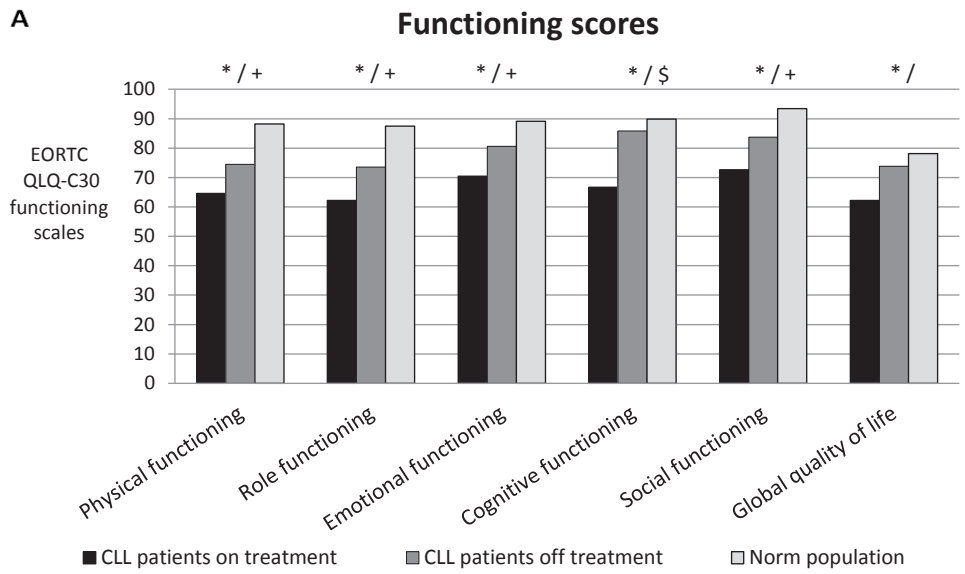
Although the combination of the observed significantly worse HRQoL for CLL/SLL patients treated with chemo- and/or immunotherapy compared to the active surveillance group, and the lack of

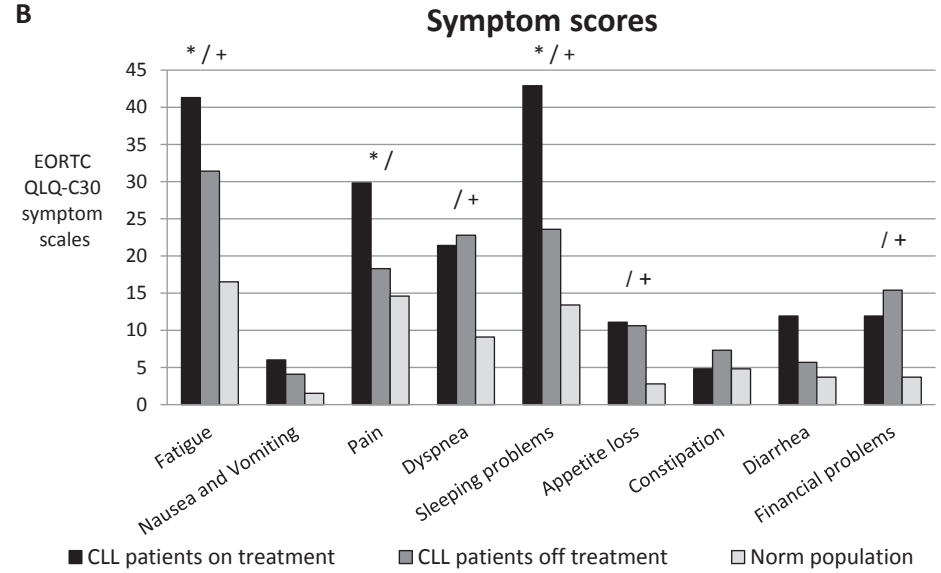
Table 3. Differences between CLL/SLL patients under active surveillance, CLL/SLL patients treated with chlorambucil and CLL/SLL patients treated with other chemo and/or immunotherapy on EORTC QLQ-C30, HADS and IOC Worry.

	Active surveillance N=68	Chlorambucil N=27	Other chemo-/ immunotherapy N=30		
EORTC QLQ-C30	Mean (SD)	Mean (SD)	Mean (SD)	p-value*	Clinical importance
Physical Functioning	87.4 (18)	69.8 (22)	75.2 (20)	<0.01[a,b]	a:medium, b:small
Role Functioning	86.5 (23)	72.8 (30)	69.4 (29)	<0.01[a,b]	a, b: small
Emotional Functioning	85.2 (19)	71.2 (31)	84.6 (20)	<0.05[a]	a: small
Cognitive Functioning	86.5 (20)	80.8 (32)	81.7 (21)	ns	
Social Functioning	92.2 (18)	79.5 (24)	82.8 (25)	<0.01[a]	a: medium
Global health status/QoL	76.6 (20)	71.9 (17)	70.6 (19)	ns	
Fatigue	22.4 (27)	35.5 (24)	31.5 (29)	ns	
Nausea / Vomiting	7.0 (18)	4.5 (9)	4.4 (11)	ns	
Pain	16.4 (26)	24.4 (28)	17.8 (25)	ns	
Dyspnea	10.8 (20)	23.1 (31)	21.1 (24)	<0.05[a]	a: medium
Insomnia	20.8 (30)	30.8 (35)	25.6 (30)	ns	
Appetite loss	10.8 (26)	8.6 (18)	12.2 (22)	ns	
Constipation	7.3 (16)	6.4 (16)	6.7 (16)	ns	
Diarrhea	8.9 (20)	9.0 (15)	5.6 (20)	ns	
Financial Problems	2.1 (8)	12.8 (27)	15.6 (27)	<0.01[a,b]	a, b: medium
% Fatigue cases	43 %	81 %	63 %	<0.01[a]	
HADS					
Anxiety	4.5 (3.7)	6.0 (4.2)	3.5 (3.7)	ns	
Depression	3.6 (3.5)	4.9 (4.1)	4.1 (4.1)	ns	
% Anxiety cases	18 %	33 %	20 %	ns	
% Depression cases	13 %	30 %	20 %	ns	
IOC+					
Worry about future	16 %	42 %	24 %	0.02[a]	
Worry about health	27 %	67 %	31 %	<0.01[a]	
Worry about cancer coming back	28 %	67 %	48 %	<0.01[a]	
Worry when new symptoms occur	21 %	46 %	43 %	0.03[a]	

Note: CLL= Chronic Lymphocytic Leukemia; SLL= Small Lymphocytic Lymphoma; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; HADS=Hospital Anxiety and Depression Scale; IOC=Impact of Cancer Scale; ns=non-significant.
*p-value is adjusted for age, sex, and number of comorbidities;[a]Difference significant between the active surveillance group and the chlorambucil group; [b]Difference significant between the active surveillance group and the other chemo/immunogroup. +Percentage of patients who answered these IOC items with "agree" or "strongly agree".
Patients were defined as a fatigue case if they had an EORTC QLQ-C30 fatigue score >21.9 (mean norm population + small clinical important difference).Patients were defined as an anxiety case if they had a HADS anxiety score >8. Patients were defined as a depression case if they had a HADS depression score >8.

Figure 3A and 3B. Differences on EORTC QLQ-C30 mean functioning and global quality of life scores (A) and symptoms scores (B) of CLL/SLL patients on treatment (N=15) and CLL/SLL patients off treatment (N=42) compared to an age- and sex-matched normative population (N=209).





Note: A higher score on functioning scores implies a better health-related quality of life, whereas a higher score on symptom scores refers to more symptoms. EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; CLL= Chronic Lymphocytic Leukemia; SLL= Small Lymphocytic Lymphoma.
*=p<0.05 and clinically important difference between CLL/SLL patients on treatment and the normative population.
+=p<0.05 and clinically important difference between CLL/SLL patients off treatment and the normative population.
$=p<0.05 and clinically important difference between CLL/SLL patients on and off treatment.

Table 4. Odds ratios with confidence intervals (CI) of the multivariate logistic regression model evaluating independent variables for worse physical functioning, high fatigue, high worry about health and high worry about future scores for CLL/SLL patients (N=136).

	Low Physical functioning (EORTC QLQ-C30)	**High Fatigue (EORTC QLQ-C30)**	**High Worry about health (IOC)**	**High Worry about future (IOC)**
	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)
Age	1.04 (0.99-1.09)	1.00 (0.96-1.04)	0.98 (0.94-1.02)	0.95 (0.90-0.99)*
Gender				
Male	Reference	Reference	Reference	Reference
Female	2.44 (0.92-6.44)	1.24 (0.53-2.87)	2.00 (0.78-5.13)	1.20 (0.42-3.40)
Comorbidity				
No comorbidities	Reference	Reference	Reference	Reference
1 comorbidity	5.11 (1.35-19.46)*	2.09 (0.73-5.97)	3.36 (0.97-11.66)	2.87 (0.71-11.66)
2 or more comorbidities	16.76 (4.29-65.43)*	2.88 (1.09-7.64)*	3.94 (1.18-13.13)*	3.45 (0.88-13.51)
Treatment				
Active surveillance	Reference	Reference	Reference	Reference
Chlorambucil	10.52 (3.00-36.91)*	5.88 (1.73-20.00)*	6.46 (2.02-20.68)*	4.79 (1.39-16.55)*
Other chemo	9.89 (2.85-34.29)*	1.98 (0.78-5.00)	0.98 (0.34-2.86)	1.51 (0.45-5.08)
Time since diagnosis	0.89 (0.63-1.26)	1.06 (0.76-1.47)	0.76 (0.50-1.15)	0.80 (0.50-1.26)

Note. *p<0.05; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; CLL= Chronic Lymphocytic Leukemia; SLL= Small Lymphocytic Lymphoma; CI=Confidence interval.
No statistically significant associations were observed between HADS anxiety and depression and these characteristics.
Low physical functioning was defined as an EORTC QLQ-C30 physical functioning score <83.2 (mean norm population-small clinically important difference) (N=52). High fatigue was defined as an EORTC QLQ-C30 fatigue score >21.9 (mean norm population + small clinically important difference) (N=70). High worry about health was defined as answered that item with agree or strongly agree (N=39). High worry about future was defined as answered that item with agree or strongly agree (N=25).

differences between CLL/SLL survivors under active surveillance and the normative population, suggests that treatment is responsible for the poorer HRQoL and not so much the disease itself, it is also possible that disease severity (stage) could explain the observed association between treatment and HRQoL, as treatment is generally not initiated until the patient experiences symptoms[28]. This explanation is strengthened by the outcomes of an RCT with relatively young patients treated with fludarabine (+/- cyclophosphamide)'[10]. In concordance with our results, it showed that CLL patients receiving treatment had a significantly impaired HRQoL on all functioning scales as well as on fatigue, nausea, and all single-items scales with the exception of pain, compared to a norm population. However, the baselines scores of these patients were similar or even worse than the scores twelve months after starting treatment, suggesting that the symptoms of disease affects HRQoL rather than therapy. On the other hand, our results also showed that patients receiving treatment scored lower than the norm population even after treatment had ended and symptoms are likely to be reduced. Therefore, we assume the poorer HRQoL among treated patients is caused by a combination of treatment effects and symptoms of active CLL. This hypothesis is confirmed by the results of a survey performed in 2006, where physical en functional well being and fatigue were related to both stage and treatment. HRQoL scores were lower among individuals with advanced stage disease[29].

Remarkably, patients treated with chlorambucil reported lower scores on physical and social functioning, dyspnea and fatigue than patients receiving other chemo-/immunotherapy. In contrast to our findings, are the results of a previous RCT that showed that during treatment patients receiving fludarabine, particularly FC, reported more HRQoL impairment compared with patients receiving chlorambucil, on role/social functioning and fatigue.[11] These differences resolved after completing therapy. There are several explanations for the discrepancies. First of all, we assessed HRQoL in a population-based setting that includes elderly and/or frail patients and patients with significant comorbidities, resulting in a representative subset of CLL/SLL patients receiving standard care, whereas patients with significant comorbidities or a short life expectancy were excluded from the trial[30]. Second, due to the observational nature of our study, the results might be biased by confounding by indication, i.e. elderly and/or frail patients with a poorer HRQoL being more likely to be treated with chlorambucil. However, we adjusted for age and comorbidity in the analyses and no statistical differences were observed in age, number of comorbidities, socio-demographic or clinical characteristics between patients treated with chlorambucil and from the other chemo group. Third, the information provided to patients in a RCT is probably more elaborate and uniform than in a population-based setting. In the latter situation patients who receive a 'simple' oral treatment (chlorambucil) might receive less information than patients who are frequently hospitalized to receive 'complex' intravenous chemo-/ immunotherapy. Receipt of less information has been associated with lower HRQoL[31].

In conclusion, despite the cross-sectional design of our study, this large population-based study with high patient response rates and detailed information about treatment, gives a quite representative overview of the symptoms and HRQoL that patients with CLL/SLL experience in all phases of disease. The recent success in prolonging survival might lead to adjustment of the current guidelines regarding starting treatment in asymptomatic patients. However,

drastic and long-lasting effects of starting treatment in CLL/SLL patients on HRQoL can not be excluded, whereas active surveillance does not seem to provoke worrying, anxiety, or depressive symptoms. Drastic, long-lasting negative effects of starting treatment on HRQoL can not be excluded, whereas active surveillance does not seem to provoke worrying, anxiety, or depressive symptoms. Further elaborate research into the impact of starting therapy on HRQoL is needed, especially in patients that are underrepresented in most clinical trials. Specifically, a larger cohort, which allows the comparison of more treatment groups and a design with questionnaires on specific moments (e.g. at diagnosis, 6 and 12 months after diagnosis, at start therapy, etc.) are preferable. Its results should be thoroughly considered during revision of treatment guidelines, as the gain in survival time by starting (a certain type of) treatment should outweigh the possible negative impact of it on patients HRQoL.

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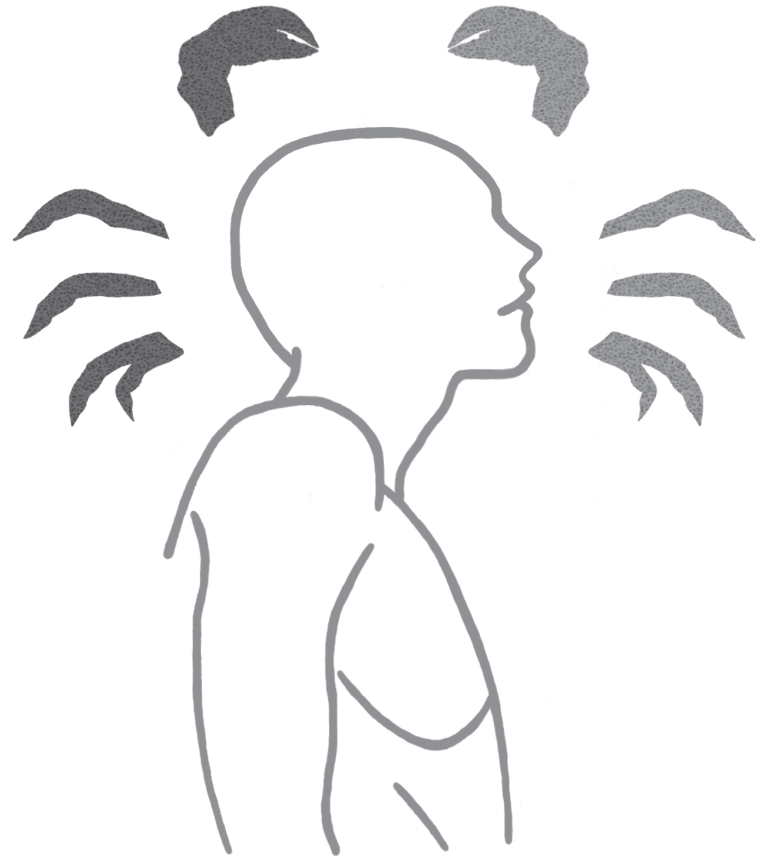
CHAPTER 6

The course of anxiety and depression for patients with Hodgkin's lymphoma or diffuse large B-cell lymphoma: a longitudinal study of the PROFILES registry



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ABSTRACT

Purpose
Prospectively assess anxiety and depression among patients with Hodgkin Lymphoma (HL) and Diffuse Large B-Cell lymphoma (DLBCL). Also, to compare its prevalence with a normative population, identify subgroups with more anxiety and depression, and assess its impact on health-related quality of life (HRQoL).

Methods
The population-based Eindhoven Cancer Registry was used to select patients diagnosed with HL or DLBCL from 1999-2010, 489 responded (T1). The HADS was completed four times (T1-T4), with a one-year interval. Linear mixed-models were used to assess the course of anxiety and depression and identify high-risk subgroups.

Results
Both anxiety and depression were reported more often by patients compared to the normative population ($p<0.05$). Over the four time points, approximately 10% of patients reported to be always and 15% reported to be sometimes anxious or depressed. Anxiety and depression did not improve in time. Patients with comorbidity and patients who were lower educated reported higher anxiety and depression scores ($p<0.05$). Younger DLBCL patients reported higher anxiety scores, whereas older DLBCL patients reported higher depression scores over time ($p<0.05$). Global health status/HRQoL was clinically relevant lower in patients with anxiety and depression and this appeared to be constant over time.

Conclusion
More HL and DLBCL patients experience anxiety and depression compared to their counterparts in the general population and it did not improve in time.

Implication for Cancer Survivors
Clinicians should be aware that former lymphoma patients with anxiety and depression have a deteriorated global health status/HRQoL and refer patients to suitable aftercare when necessary.

INTRODUCTION

Survival for patients with Hodgkin Lymphoma (HL) and Diffuse Large B-Cell Lymphoma (DLBCL) has improved dramatically over the past decades. Currently, the overall 5-year relative survival rate (2002-2008) is 81-90% for HL and 71-82% for DLBCL[1, 2]. As lymphoma patients survive longer, they often face long-term effects caused by their treatment, such as treatment-induced secondary tumors and cardiovascular disease[3-10]. Apart from these adverse physical effects, many lymphoma patients also report long-term psychosomatic and psychosocial problems, such as depression and anxiety[11-19].

Studies focusing on depression and anxiety in lymphoma patients observed prevalence rates of depression between 2-35%[14, 20-22] and rates of anxiety between 12-42%[14, 20-23], with also differences in assessment methods, as well as in patients and tumor characteristics. Furthermore, comparisons with normative populations are scarce. Little is known about the longitudinal course of anxiety and depression in these patients during their post-treatment follow-up and their return to normal life and the impact of it on health-related quality of life (HRQoL).

The aims of the present study were to (1) compare the prevalence of anxiety and depression of HL and DLBCL patients with an age- and sex-matched normative population, (2) prospectively assess the course of anxiety and depression following primary treatment and identify subgroups of patients who report higher or lower scores and (3) assess the relation of anxiety and depression with global health/HRQoL. We hypothesised that prevalence rates of anxiety and depression would be higher in HL and DLBCL patients compared to the normative population. Furthermore, anxiety and depression would decrease during follow-up with longer survival.

DESIGN AND METHODS

Lymphoma patients
This study is part of a longitudinal population-based survey among HL and DLBCL patients registered by the Eindhoven Cancer Registry (ECR). The ECR records data on all patients who are newly diagnosed with cancer in the southern part of the Netherlands, an area with 2.3 million inhabitants, 18 hospital locations and 2 large radiotherapy institutes. The ECR was used to select patients who were diagnosed with HL or DLBCL between January 1st, 1999 and July 1st, 2010 as defined by the International Classification of Diseases for Oncology-3 codes (ICD-O-3)[24] and were 18 years or older at time of diagnosis. Patients who had deceased were excluded through linkage with the database of the Central Bureau for Genealogy. Ethical approval for the study was obtained from a certified Medical Ethics Committee (of the Maxima Medical Centre in Veldhoven, The Netherlands; number 0734).

Study measures
The Hospital Anxiety and Depression Scale (HADS)[25-27], measures symptoms in separate subscales of 7 items each. Answers range from 0 to 3 and scores for each subscale are calculated by

addition of the items, with a higher score meaning more anxiety or depression. A score on either subscale of ≥8 indicates a substantial level of anxiety or depression[25-27]. This questionnaire measures the extent to which patients experience anxiety or depressive symptoms and can not diagnose a clinical anxiety or depressive disorder. The term depression in this manuscript does not imply a diagnosis of a clinical depression. Estimated reliability was assessed at T1 for both patients' samples by Cronbach's alpha. For the HL sample, Cronbach's alpha was 0.87 for the anxiety and 0.85 for the depression scale and for the DLBCL sample, Cronbach's alpha was 0.82 for the anxiety and 0.84 for the depression scale.

The 'global health status and Quality of Life scale' of the Dutch validated version of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30) was used to assess global health status/HRQoL. It consists of two questions, i.e. "How would you rate your overall health during the past week?" and "How would you rate your overall quality of life during the past week?" with a 7-point likert scale as answer categories. After linear transformation, the scale ranges in score from 0 to 100, whereby a higher score implies a better global health status/HRQoL[28].

Comorbidity at time of survey was categorized according to the adapted Self-administered Comorbidity Questionnaire (SCQ)[29]. Patients' marital status and educational level were also assessed in the questionnaire. Clinical information was available from the ECR that routinely collects data on tumor characteristics, including date of diagnosis, tumor grade, histology, Ann Arbor stage[30], primary treatment, and patients background characteristics, including gender and date of birth.

Data collection

Data collection was done within PROFILES (Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship). PROFILES is a registry for the study of the physical and psychosocial impact of cancer and its treatment from a dynamic, growing population-based cohort of both short and long-term cancer survivors. PROFILES contains a large web-based component and is linked directly to clinical data from ECR. Details of the data collection method have been previously described[31]. Data from the PROFILES registry are available for non-commercial scientific research, subject to study question, privacy and confidentiality restrictions, and registration (www.profilesregistry.nl).

In May 2009, patients diagnosed between January 2004 and January 2009 were included in the study and received the first questionnaire. In November 2009 and in May 2011 (last cohort included) patients newly diagnosed up to July 1st 2010 were subsequently invited to participate. Thus three cohorts in which all patients received the subsequent questionnaires with a one year interval starting from time of enrollment. The first cohort is assessed 4 times, the second cohort is measured 3 times, and the third cohort is measured 2 times (see Figure 1).

Normative population

The normative population was selected from a reference cohort of 2040 individuals from the general Dutch population (CentER panel). This cohort is representative for the Dutch-speaking population in the Netherlands[32]. The set of questionnaires completed by this normative population in November 2011 included the HADS, SCQ, and data on socio-demographics. From

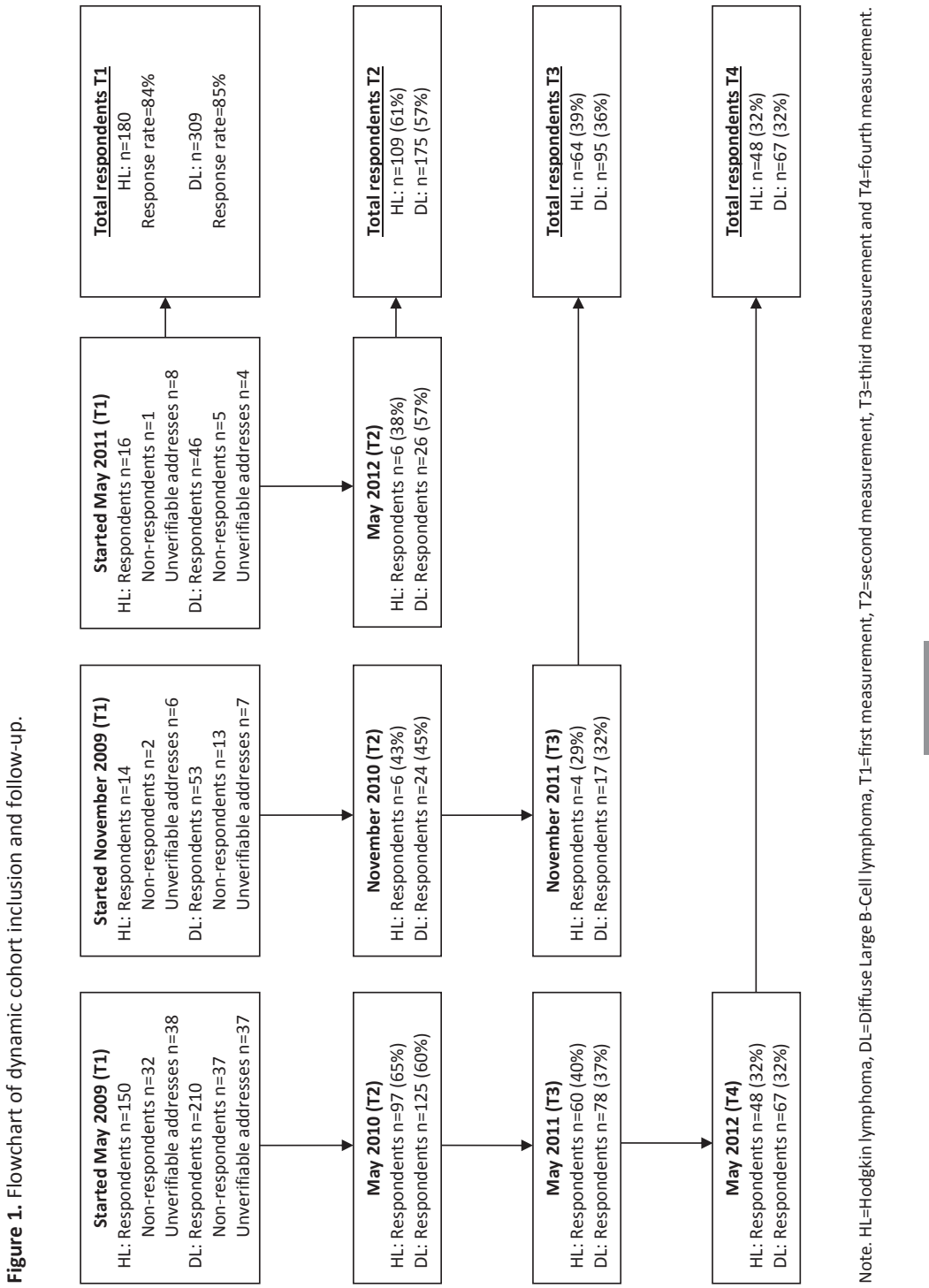


Figure 1. Flowchart of dynamic cohort inclusion and follow-up.

Note. HL=Hodgkin lymphoma, DL=Diffuse Large B-Cell lymphoma, T1=first measurement, T2=second measurement, T3=third measurement and T4=fourth measurement.

this normative population, two age- and sex-matched selections were made to compare anxiety and depression with the two patient groups, one for HL (N=360) and one for DLBCL (N=425). For matching, ten strata were formed using sex and age (5 categories). Within each stratum a maximum number of persons from the reference cohort were randomly matched according to the strata frequency distribution of the patients. This resulted in 360 matched cancer-free individuals for the 180 HL patients and 425 matched cancer-free individuals for the 309 DLBCL patients.

Statistical analyses

Differences in baseline socio-demographic and clinical characteristics between respondents and non-respondents (never completed a questionnaire) or patients with unverifiable addresses were compared with a chi-square or t-test, where appropriate. Differences in baseline socio-demographic and clinical characteristics between patients who completed one questionnaire or patients who completed more questionnaires were also compared with a chi-square or t-test, where appropriate.

Prevalence rates of anxiety and depression from the HL and DLBCL patients were compared with an age- and sex-matched Dutch normative population using chi-square tests. We categorized patients as 'always anxious/depressed' with a HADS anxiety or depression score ≥8 on every measurement (T1-T4) and 'never anxious/depressed' if patients never reported a score ≥8 at every measurement. Patients who scored ≥8 at some of the four measurements were categorized as 'sometimes anxious/depressed'.

The course of anxiety and depression was analyzed separately using linear mixed-effects models (i.e., covariance pattern model with an unstructured error covariance matrix and maximum likelihood estimation)[33]. Time was analyzed as a regular categorical predictor with four levels (i.e. four time points). Socio-demographic (age, sex, marital status, education level) and clinical variables (comorbidity, treatment type, stage of disease, time since diagnosis) were determined a priori and analyzed as time-invariant predictors (i.e. baseline characteristics were used). The interaction of sex and age was tested separately and interactions were only maintained in the final model if they were significantly associated with anxiety and/or depression. In order to correctly interpret all model parameters, all continuous variables have been grand-mean centered[33, 34].

The course of global health status/HRQoL was also analyzed using linear mixed-effects models (i.e., covariance pattern model with unstructured error covariance matrix and maximum likelihood estimation)[33]. Anxiety and depression scores were analyzed as continuous time-varying predictors[33] (separate models) and sex, age and number of comorbidities were entered as covariates into both models.

Analyses were performed in IBM SPSS 19.0 and SAS (version 9.3 for Windows; SAS Institute Inc., Cary, NC) using significance level of α=.05. Clinically relevant differences were determined using the evidence-based guidelines for interpretation of the EORTC QLQ-C30 between groups35, a difference ≥4 indicates at least a small clinical relevant difference on the global health status/HRQoL scale. Norman's 'rule of thumb' was used for the HADS whereby a ± 0.5 SD difference (i.e. 1.7 points) indicates a threshold of discriminating change in scores[36, 37].

RESULTS

Patients and normative population

Figure 1 shows the number of patients throughout the measurements. One hundred eighty HL and 309 DLBCL patients completed the first questionnaire (T1, 85%). Subsequently, among HL patients, 109 (61%) completed the second measurement, 64 (39%) the third and 48 (32%) also the fourth measurement. Among DLBCL patients, 175 (57%) completed the second measurement, 95 (36%) the third and 67 (32%) also the fourth measurement. Mean age at T1 was 46.1 years for HL and 63.6 years for DLBCL patients with a mean time since diagnosis of 4.7 years and 3.5 years respectively (Table 1). Combination of radiotherapy and chemotherapy was most frequently received in HL patients (55%) and chemotherapy alone in DLBCL patients (67%). Half of HL patients and two-third of DLBCL patients reported one or more comorbid conditions, the most common were arthritis and back pain.

Despite matching on age and sex, patients with DLBCL more often reported to have one comorbid condition and less often reported to have two comorbid conditions compared to the normative population. The average number of comorbidities however did not differ between these groups (Table 1). DLBCL patients were furthermore lower educated and more often married than the normative population. No differences on socio-demographic characteristics were observed between HL patients and the normative population.

Quality of data

Non-response analysis

At T1, HL patients who responded were more often female than HL patients who did not respond or had unverifiable addresses (45% versus 34% and 27% was female; p=0.049). DLBCL patients who responded were more often male than DLBCL patients who did not respond or had unverifiable addresses (65% versus 44% and 44%; p<0.01). They had also more often received chemotherapy alone compared to DLBCL non-respondents and patients with unverifiable addresses (67% versus 51% and 50%; p<0.01). No statistically significant differences between respondents, non respondents and patients with unverifiable addresses were observed for age, time since diagnosis, and stage (data not shown).

Analysis between patients who completed one or more questionnaires

HL patients who completed more questionnaires had a significantly longer mean time since diagnosis at time of first enrollment than HL patients who completed only one questionnaire (5.2 vs. 3.9 years, p<0.01). No statistically significant differences were observed between these groups on anxiety ($\overline{X}$ =5.0 versus $\overline{X}$ =4.4, p=0.35) or depression scores ($\overline{X}$ =3.7 versus $\overline{X}$ =3.6, p=0.87) or for sex, age, stage, primary treatment, comorbidities, marital status, and educational level. Also for DLBCL patients no statistically significant differences were observed between patients who completed one or more questionnaires for anxiety ($\overline{X}$ =4.0 versus $\overline{X}$ =4.3, p=0.38) or depression scores ($\overline{X}$ =4.2 versus $\overline{X}$ =4.3, p=0.77) or for the other above mentioned characteristics.

Table 1. Socio-demographic and clinical characteristics of HL (N=180) and DLBCL (N=308) survivors, and respondents of an age- and sex-matched normative population (N=360 for HL and N=425 for DLBCL).

	HL survivors N=180	HL matched norm population N=360		DLBCL survivors N=309	DLBCL matched norm population N=425	
	N (%)	N (%)	p-value	N (%)	N (%)	p-value
Sex			0.90			0.95
Male	99 (55)	200 (56)		201 (65)	282 (66)	
Female	81 (45)	160 (44)		108 (35)	143 (34)	
Age at time of survey: mean (SD)	46.1 (16)	48.3 (16)	0.12	63.6 (13)	63.7 (13)	0.79
<35 years	52 (29)	74 (21)		11 (4)	14 (3)	
35-44 years	40 (22)	81 (23)		16 (5)	24 (6)	
45-54 years	34 (19)	69 (19)		45 (15)	59 (14)	
55-64 years	28 (16)	70 (19)		68 (22)	88 (21)	
65-74 years	15 (8)	46 (13)		103 (33)	152 (36)	
75+ years	11 (6)	20 (6)		66 (21)	88 (21)	
Stage at diagnosis						
I	32 (18)			106 (35)		
II	94 (53)			74 (24)		
III	35 (20)			61 (20)		
IV	18 (10)			63 (21)		
Primary treatment						
Radiotherapy alone	5 (3)			5 (2)		
Chemotherapy alone	74 (41)			208 (67)		
Radio and chemotherapy	99 (55)			85 (28)		
Years since diagnosis: mean (SD)	4.7 (2.9)			3.5 (2.4)		
0-1 years	9 (5)			30 (10)		
1-3 years	55 (31)			122 (39)		
3-5 years	36 (20)			84 (27)		
5-7 years	33 (18)			39 (13)		
7-10 years	47 (26)			34 (11)		
Self-reported comorbidity: mean (SD)	1.0 (1.3)	1.0 (1.4)	0.52	1.3 (1.2)	1.4 (1.4)	0.15
No comorbid condition	84 (49)	167 (46)	0.95	89 (31)	144 (34)	0.14
1 comorbid condition	49 (29)	99 (28)	0.95	101 (35)	104 (24)	0.01
2 or more comorbid conditions	38 (22)	94 (26)	0.20	98 (34)	177 (42)	<0.01
Frequent reported comorbid conditions						
Arthritis	23 (15)	44 (12)	0.37	62 (27)	101 (24)	0.41
Back pain	29 (20)	89 (25)	0.21	66 (29)	122 (29)	0.96
Partner			0.38			0.04
Yes	136 (76)	284 (79)		245 (80)	313 (74)	
No	44 (24)	76 (21)		60 (20)	112 (26)	
Education level[$]			0.14			<0.01
Low	14 (8)	15 (4)		51 (17)	22 (5)	
Medium	109 (61)	212 (59)		176 (59)	240 (57)	
High	56 (31)	131 (37)		73 (24)	162 (38)	
HADS anxiety (mean (SD)	4.8 (4)	3.8 (3)	<0.01	4.1 (4)	3.4 (3)	<0.01
HADS depression (mean (SD)	3.7 (4)	3.4 (3)	0.41	4.3 (4)	3.9 (3)	0.08
EORTC HRQoL (mean (SD)	76.9 (18)			74.7 (20)		

Note. HL=Hodgkin lymphoma, DL=Diffuse Large B-Cell lymphoma; [$]Education levels included low= no/primary school; medium= lower general secondary education/vocational training; or high= pre-university education/ high vocational training/university.

Prevalence of anxiety and depression

The prevalence of anxiety in HL patients on T1 was 24% compared to 13% in the normative population (p<0.01) and the prevalence of depression was 18% compared to 12% in the norm (p=0.045; Figure 2). Among DLBCL patients, the prevalence of anxiety on T1 was 17% compared to 11% in the normative population (p<0.01) and the prevalence of depression was 19% compared to 14% in the norm (p=0.044; Figure 2).

On average over the four time points, 13% of HL and 8% of DLBCL patients were always anxious, and 18% and 17%, respectively was sometimes anxious. Furthermore, 11% of HL and 9% of DLBCL patients were always depressed, whereas 14% and 18% respectively was sometimes depressed.

Factors longitudinally associated with anxiety and depression

Hodgkin lymphoma

No change was observed in HL patients' anxiety or depression mean scores during the four assessments (p=0.38 and p=0.56, respectively; Table 2). HL patients with comorbid diseases reported higher anxiety and depression scores over time (both p<0.01). Furthermore, higher depression scores over time were reported by HL patients with a low education level (p<0.01) and by younger women and older men (interaction effect sex*age p<0.01). No association was observed between time since diagnosis, sex, treatment or disease stage and anxiety or depression scores.

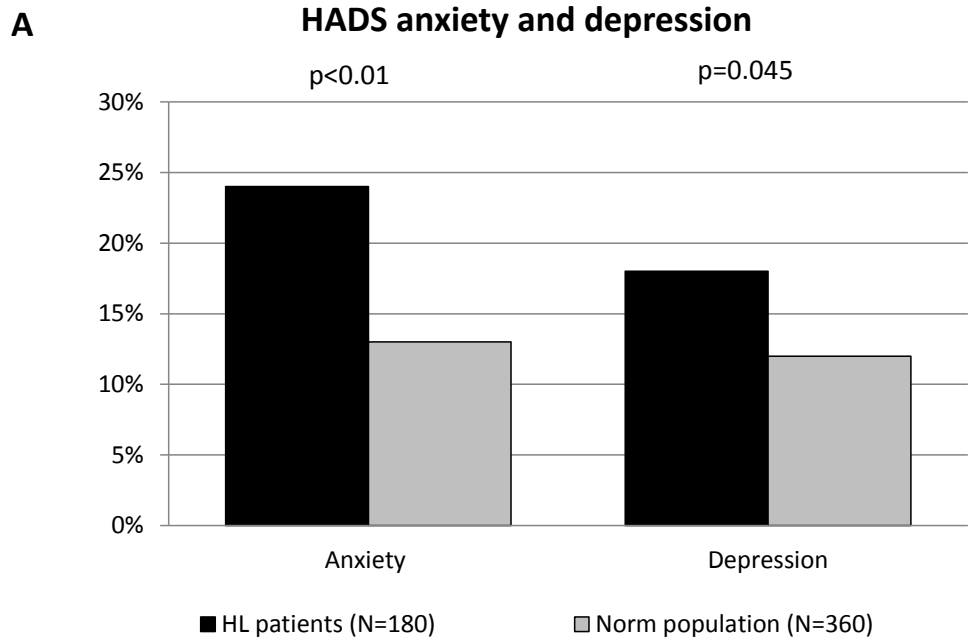
Diffuse Large B-Cell Lymphoma

For DLBCL patients no time effect was observed for anxiety (p=0.48) but a significant effect of time was found for depression (p<0.01; Table 2). The largest change for depression was observed between the first (T1) and last assessment (T4), although this mean change of 1.1 point was not clinically relevant (i.e. not higher than the 0.5 SD of 1.7). Younger DLBCL patients reported more anxiety (p=0.03), whereas depression scores became higher in older DLBCL patients (p=0.02). In addition, DLBCL patients with a low or medium education level and patients with comorbid diseases reported more anxiety and depression over time (all p<0.05). No longitudinal association was observed between time since diagnosis, sex, marital status, treatment or disease stage and anxiety or depression scores.

Anxiety and depression in relation with HRQoL

Of HL and DLBCL patients who always reported high anxiety scores (score ≥8 on all measurements), global health status/HRQoL mean scores were on average 18 to 29 points lower among patients who never reported anxiety (Figure 3). Patients who always reported high depression scores (score ≥8 on all measurements) reported global health status/HRQoL mean scores that were on average 28 to 34 points lower than patients who never reported depression scores. These differences in global health status/HRQoL between patients always and never reporting anxiety/depression scores were clinically very relevant, i.e. >15 points difference[35]). Linear mixed-effect models supported this observation of the raw data and showed that higher levels of anxiety and depression were statistically significant associated over time with lower global health status/HRQoL (between-subject effects βs between -1.9 and -3.4; p<0.01, not tabulated).

Figure 2. Prevalence of HADS anxiety and depression among HL (A) and DLBCL (B) patients on T1 and of the age- and sex-matched normative populations.



Note. HL= Hodgkin Lymphoma, DLBCL= Diffuse Large B-Cell Lymphoma; HADS=Hospital Anxiety and Depression Scale. HADS Anxiety was defined as a score ≥8; HADS Depression was defined as a score ≥8.

Table 2. Final model of a priori determined time, socio-demographic and clinical factors associated with HADS anxiety and depression for HL and DLBCL patients.

	HL				DLBCL			
	Anxiety		Depression		Anxiety		Depression	
	Beta	p-value	Beta	p-value	Beta	p-value	Beta	p-value
Time variables								
Time		0.38		0.56		0.48		<0.01
T4 versus T1	0.5		-0.06		-0.5		-1.1	**<0.01**
T4 versus T2	0.4		0.2		-0.4		-0.8	**0.04**
T4 versus T3	0.6		-0.02		-0.3		-0.9	**0.02**
Time since diagnosis#	-0.02	0.84	0.04	0.58	-0.01	0.93	0.02	0.85
Sociodemographic variables								
Age#	-0.03	0.17	**-0.05^**	**0.04^**	-0.04	0.03	0.04	**0.02**
Sex (men)	0.02	0.97	**0.7^**	**0.14^**	-0.3	0.51	0.7	**0.10**
Married (yes)	-1.0	0.07	-0.8	0.08	0.01	0.98	0.5	**0.35**
Education		0.09		<0.01		<0.01		<0.01
High-low	2.4		4.5	<0.01	2.9	<0.01	2.1	**<0.01**
High-mid	0.8		0.9	0.06	1.1	0.02	1.4	**<0.01**
Sex*age#		-	0.09	**<0.01**		-		-
Clinical variables								
Comorbidities#	0.6	<0.01	0.4	<0.01	0.6	<0.01	0.4	**<0.01**
Radiotherapy (yes)	-0.8	0.16	-0.8	0.10	0.04	0.94	0.5	**0.37**
Chemotherapy (yes)	0.8	0.60	2.1	0.13	0.01	0.99	0.97	**0.32**
Stage		0.65		0.89		0.64		0.22
Stage I versus II	-1.1		-0.3		0.5		1.1	
Stage I versus III	-1.1		0.4		-0.3		0.2	
Stage I versus IV	-0.6		0.06		0.1		-0.07	

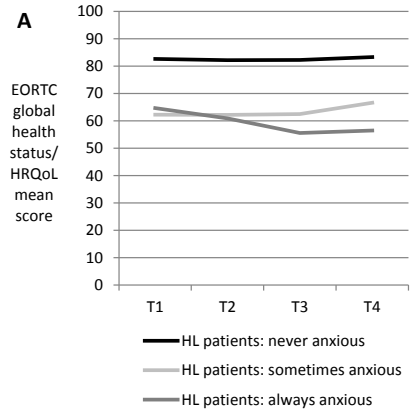
Note. #Continuous variables are grand-mean centered; ^ANOVA tests of main effects are not to be interpreted because of interaction effect. The interaction of sex and age was tested separately and interactions were only maintained in the final model if they were significantly associated with anxiety and/or depression. This was only the case for HL depression. All other presented models are without the interaction factor. HL= Hodgkin Lymphoma, DLBCL= Diffuse Large B-Cell Lymphoma; HADS=Hospital Anxiety and Depression Scale.

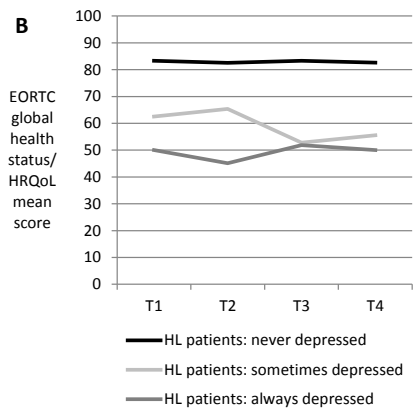
DISCUSSION

Anxiety and depression were reported more often by HL and DLBCL patients compared to the age- and sex-matched normative populations, i.e. patients reported rates between 17-24% and the normative populations between 11-14%, which confirms our hypothesis. Over the four time points, approximately 10% of HL and DLBCL patients reported to be always anxious or depressed and an additional 15% sometimes. Importantly, global health status/HRQoL was relevantly, up to 34 points, lower in patients with anxiety or depression and appeared to be constant over time.

Up to now only four studies, three cross-sectional and one longitudinal, focused on anxiety and depression among lymphoma patients of which two were conducted more than 15 years ago. Three of these studies also observed higher anxiety or depression scores among lymphoma patients compared to a normative population[14, 21, 23]. The observed prevalence of anxiety between

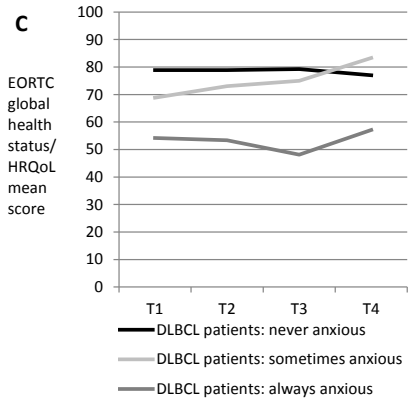
Figure 3. EORTC global health status/HRQoL observed mean scores over time for HL (A) and DLBCL (C) patients who were never, sometimes, or always anxious and for HL (B) and DLBCL (D) patients who were never, sometimes, or always depressed.

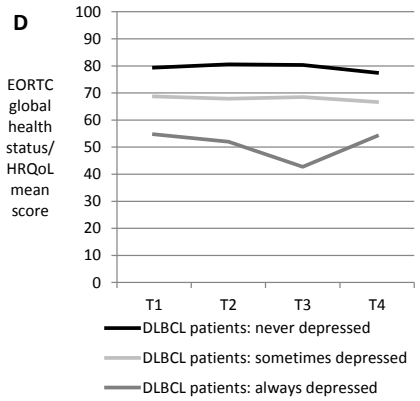




	T1	T2	T3	T4
HL patients: never anxious	N=77	N=74	N=45	N=33
HL patients: sometimes anxious	N=21	N=20	N=12	N=8
HL patients: always anxious	N=15	N=15	N=7	N=7

	T1	T2	T3	T4
HL patients: never depressed	N=85	N=81	N=48	N=38
HL patients: sometimes depressed	N=16	N=16	N=8	N=5
HL patients: always depressed	N=12	N=12	N=8	N=5





	T1	T2	T3	T4
DLBCL patients: never anxious	N=138	N=132	N=73	N=50
DLBCL patients: sometimes anxious	N=27	N=26	N=18	N=15
DLBCL patients: always anxious	N=17	N=17	N=4	N=2

	T1	T2	T3	T4
DLBCL patients: never depressed	N=131	N=125	N=71	N=51
DLBCL patients: sometimes depressed	N=30	N=30	N=18	N=14
DLBCL patients: always depressed	N=21	N=20	N=6	N=2

Note. Only scores of HL/DLBCL patients who completed at least two measurements are included in these figures. The higher the EORTC global health status/HRQoL mean score, the better the health-related quality of life. Patients were categorized as 'always anxious/depressed' as they reported a HADS anxiety or depression score ≥8 on every measurement (T1-T4) and 'never anxious/depressed' as they never reported a score ≥8 on every measurement. Patients that scored ≥8 on some of the measurements were categorized as 'sometimes anxious/depressed'.

17-24% and depression between 18-19% was also in line with a longitudinal study using the HADS scale that studied lymphoma patients until one year after diagnosis[21]. Other cross-sectional studies reported prevalence rates of 15-42% for HADS anxiety and 4-35% for HADS depression[14, 22].

In the present study, patients showed no improvement in time in anxiety or depression. One cross-sectional study among 459 Norwegian HL patients observed that patients 7-10 years after diagnosis reported higher anxiety and depression compared to patients 3-6 years after diagnosis[14], contrasting our hypothesis. So, it seems that anxiety and depression are not limited to the first few years after diagnosis.

DLBCL patients who were lower educated, reported anxiety more often and depression was reported more often by both lower educated HL and DLBCL patients. This is in line with a cross-sectional study among 459 HL patients in Norway[14]. We furthermore observed more depression among older DLBCL patients which was in line with a longitudinal study among lymphoma patients[21]. We observed no association between primary treatment and stage of disease and anxiety/depression, which was in line with a Norwegian study among HL patients[14].

The difference in prevalence of anxiety and depression was larger between the age and sex-matched normative population and HL patients than the difference between the norm and the DLBCL patients. This might suggest that since the HL patients group was on average 18 years younger, being diagnosed with lymphoma on an earlier age has a greater impact. Larger differences between younger lymphoma patients compared to a normative population were also observed with respect to HRQoL[38]. An explanation might be that older patients may have better coping strategies through more life experience and they are likely to be faced with lower work-related and social demands. It is also possible that, as more health events occur with aging, cancer may not have such a specific impact on patients mental health relative to comparably aged adults without cancer who experience other health issues impacting mental health.

The strong relation observed between anxiety and depression and global health status/HRQoL appeared consistent over time, resulting in clinically relevant lower global health status/HRQoL in patients with anxiety or depression. This stipulates the importance for recognition and referral for treatment of anxiety and depression in order to maintain HRQoL. Furthermore, a systematic review showed that adequate information provision was associated with lower levels of anxiety and depression in cancer patients[39]. Since up to one-third of lymphoma patients was not satisfied with the amount of received information and at least a quarter wanted more information, there might be room for improvement[40]. Moreover, patients with depressive symptoms seem to have a twofold risk for all-cause mortality, even after adjustment for major clinical predictors[41].

The current study has some limitations. We do not know if patients did not participate because of poor health or rather absence of symptoms. Moreover, detailed information on additional treatments after primary treatment or on receiving treatments at the time of completion of the questionnaire is not available. The longitudinal design provided important information about the course of anxiety and depression. In addition, data of an age- and sex-matched normative

population makes is possible to determine what the 'normal' levels of anxiety and depression are for people without cancer. Furthermore, the population-based sampling frame and the ten-year range in elapsed time since diagnosis facilitates to extrapolate the results to a broad range of lymphoma patients in the population.

In conclusion, up to approximately a quarter of both HL and DLBCL patients can experience persistent anxiety and depression long after diagnosis and treatment. Clinicians might be more aware that former lymphoma patients with anxiety and depression have a lower global health status/HRQoL and refer patients to suitable aftercare when necessary. Special attention should go to patients with comorbidities and patients who are lower educated as they were more likely to report anxiety and depression over time.

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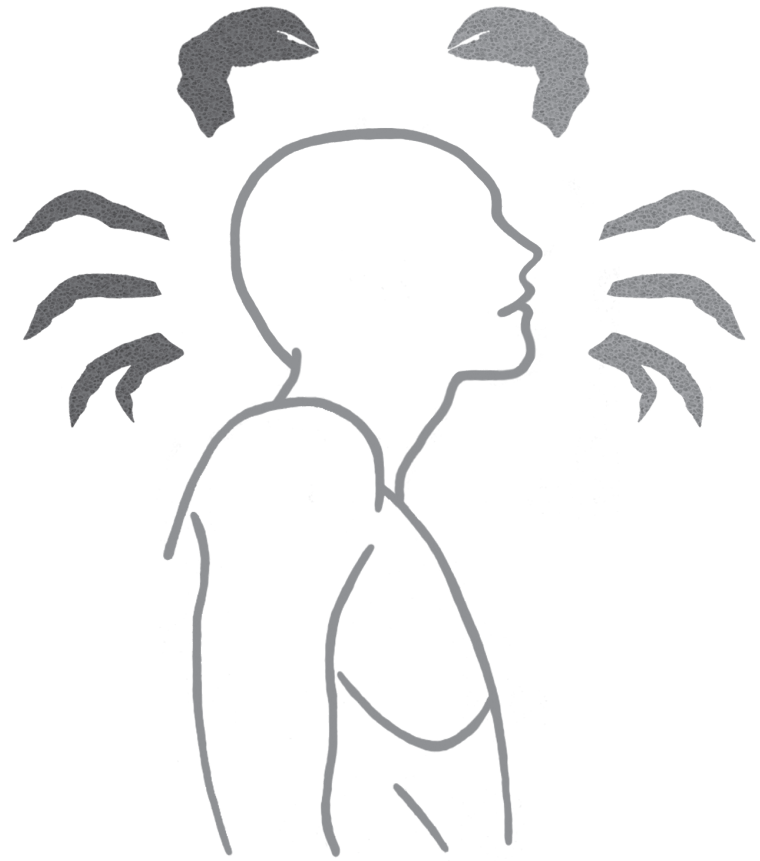
CHAPTER 7

A high level of fatigue among long-term survivors of non-Hodgkin's lymphoma: results from the longitudinal population-based PROFILES registry in the south of the Netherlands



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ABSTRACT

The course of fatigue and quality of life in survivors of non-Hodgkin's lymphoma is unknown. The aims of this study were, therefore, to assess fatigue and quality of life in patients with non-Hodgkin's lymphoma following primary treatment, compare fatigue and quality of life in these patients with those of an age- and sex matched normative population to assess the severity of concerns and identify associations with fatigue of survivors who remained fatigued. The population-based Eindhoven Cancer Registry was used to select all patients diagnosed with non-Hodgkin's lymphoma from 1999-2009. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire and the Fatigue Assessment Scale were completed once by 824 survivors of non-Hodgkin's lymphoma (80% response rate); 434 survivors completed these questionnaires again 1 year later. Survivors of non-Hodgkin's lymphoma reported more clinically relevant fatigue up till 10 years post-diagnosis compared to a normative population ($P<0.001$). Mean fatigue scores remained fairly stable over time (T1: x=28, SD=26; T2: x=30, SD=27, P=0.14): 22-28% of survivors reported deterioration, 19-23% reported improvement and 44-54% reported constant fatigue. Survivors who reported constant fatigue were more often diagnosed with stage IV disease and had more comorbid diseases. They were additionally more often female and divorced. Having comorbidities and being without a partner were also associated with constant fatigue in the normative population. In conclusion, six out of every ten responding non-Hodgkin's lymphoma survivors reported a high level of fatigue up till 10 years after diagnosis. Mean fatigue scores remained stable over time and survivors reporting constant fatigue more often had stage IV disease at diagnosis and comorbidities.

INTRODUCTION

As a result of new therapies, the survival of patients with non-Hodgkin's lymphoma (NHL) has improved considerably. Although the statistics vary, depending on the type of NHL, stage of disease at diagnosis, treatment, and age of the patient, the overall 5-year relative survival rate for all types of NHL (2001–2007) is 50–62%[1]. A person diagnosed with cancer is defined as a survivor from the moment of diagnosis through the rest of his or her life[2]. The number of NHL survivors in the USA increased from approximately 347,000 in 2001 to approximately 454,000 in 2008[1]. In the Netherlands there were approximately 19,600 NHL survivors at the end of 2008[3, 4].

As many cancer survivors live longer, they are at risk of adverse physical and psychosocial long-term effects, secondary tumors, and recurrence as a result of their cancer and/or of their medical treatments[5-7]. These long-term effects, such as fatigue, depression, marital disruption, and problems with infertility, can have a negative influence on survivors' health-related quality of life (HRQoL)[8-12].

In the last decades, more attention is being paid to HRQoL after cancer diagnosis. Some studies have investigated HRQoL and fatigue in NHL survivors[13-21], but almost all used a cross-sectional approach (only one measurement at a defined time)[13, 17-21]. However, the longitudinal course of fatigue and HRQoL in patients with NHL and their return to normal life remains largely unknown. The aims of the present study were, therefore, to: (i) assess fatigue and HRQoL twice following primary treatment, (ii) compare fatigue and HRQoL with an age- and sex matched normative population to assess the severity of the concerns, and (iii) identify associations with fatigue in survivors who remained fatigued.

DESIGN AND METHODS

Setting and population

This study is part of a dynamic, longitudinal, population-based survey among NHL survivors registered with the Eindhoven Cancer Registry (ECR) of the Comprehensive Cancer Centre South (CCCS). The ECR records data on all patients who are newly diagnosed with cancer in the southern part of the Netherlands, an area with 2.3 million inhabitants, 18 hospital locations and two large radiotherapy institutes. The ECR was used to select all patients who were diagnosed with NHL between January 1st, 1999 and July 1st, 2009. We included all patients with indolent (including chronic lymphocytic leukemia) and aggressive B-cell NHL as defined by the International Classification of Diseases for Oncology-3 (ICD-O–3) codes[22].

Participants aged ≥85 years at time of the first measurement were excluded, because they would likely have had difficulty in completing self-administered questionnaires without assistance. To exclude patients who had died, our database was linked on every measurement with the database of the Central Bureau for Genealogy, which collects data on all deaths of Dutch citizens through the civil municipal registries. Ethical approval for the study was obtained from a local, certified Medical Ethics Committee.

Study measures

We used the Dutch validated version of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30) to assess HRQoL and fatigue. Answer categories range from one (not at all) to four (very much). After linear transformation, all scales and single item measures range in score from 0 to 100. A higher score on function scales and global health and quality of life scales implies a better HRQoL, whereas for symptoms a higher score refers to more symptoms[23].

Fatigue was also assessed with the Fatigue Assessment Scale (FAS), a questionnaire consisting of ten items: five questions exploring physical fatigue and five questions exploring mental fatigue. The response scale is a 5-point scale (1 never to 5 always) and scores can range from 10 to 50. A score >21 indicates substantial fatigue. The psychometric properties are good[24, 25].

Comorbidity at the time of the survey was categorized according to the adapted Self-administered Comorbidity Questionnaire (SCQ)[26]. Survivors' marital status and educational level were also assessed in the questionnaire. Clinical information was available from the ECR which routinely collects data on tumor characteristics, including date of diagnosis, tumor grade, histology, Ann Arbor stage[27], primary treatment, and patients background characteristics, including gender and date of birth.

Data collection

Data were collected within PROFILES (Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship). PROFILES is a registry for the study of the physical and psychosocial impact of cancer and its treatment from a dynamic, growing population-based cohort of both short and long-term cancer survivors. PROFILES contains a large web-based component and is linked directly to clinical data from the ECR. Details of the data collection method have been described previously[28].

From May until November 2009, patients diagnosed between 6 months and 10 years previously received the baseline questionnaire (T1). A year later, patients who were willing to participate again received a 1-year follow-up questionnaire (T2).

EORTC QLQ-C30, SCQ, marital status and educational level data were also collected from an age-and sex-matched normative population[29] for comparison with the NHL survivors.

Statistical analyses

All statistical analyses were performed using SAS (version 9.1 for Windows; SAS Institute Inc., Cary, NC, USA). P values <0.05 were considered statistically significant. Clinically relevant differences were determined using evidence-based guidelines for the interpretation of EORTC QLQ-C30 scores between groups[30] and changes in scores[31] and Norman's 'rule of thumb' was used for the FAS whereby a ± 0.5 SD difference indicates a threshold of discriminating change in HRQoL scores[32].

Differences in socio-demographic and clinical characteristics between respondents and non-respondents or patients with unverifiable addresses and patients who completed one or two questionnaires were compared with a chi-square or t-tests, where appropriate. The mean EORTC QLQ-C30 scores among the NHL survivors were compared with those from an age- and sex-matched Dutch normative population using independent sample t-tests. Paired sample t-tests

were performed to compare the mean EORTC QLQ-C30 (both NHL survivors and the normative population) and FAS (only NHL survivors) Fatigue scale scores on T1 and T2.

Multivariate logistic regression analyses were carried out to investigate the independent association between the socio-demographic and clinical variables and constant fatigue (versus not constant fatigue). The "constant fatigue group" was defined by survivors/respondents of the normative population who had a Fatigue score >22 on both T1 and T2 for the EORTC QLQ-C30 (i.e. at least a small, clinically relevant higher score than that of the normative population[30]) versus the group who did not have a fatigue score >22 on both T1 and T2. With respect to the FAS, the 'constant fatigue group' was defined by survivors who had a Fatigue score >21 on both T1 and T2 (i.e. indication of substantial fatigue[25]) versus the group who did not have a fatigue score >21 on both T1 and T2.

RESULTS

Characteristics of the patients and normative population

Eight hundred and twenty-four NHL survivors completed the first questionnaire (80% response rate). Subsequently, 434 (53%) survivors completed this questionnaire again 1 year later, which represents 36% of the total group of NHL survivors. Of the 1731 respondents of the normative population who completed the EORTC QLQ-C30, 602 could be age- and sex-matched with the NHL survivors. Of those 602, 515 (86%) respondents completed the questionnaire again 1 year later. Survivors with unverifiable addresses were more often female and younger compared to respondents, and non-respondents were more often diagnosed with indolent NHL and less often diagnosed with stage I disease (Table 1).

The mean age at completion of the baseline survey was 63.5 years with a mean time since diagnosis of 4.2 years. Chemotherapy was the most frequent primary treatment (42%; Table 1). Two-thirds of survivors reported one or more comorbid conditions, the most common being arthritis, back pain and hypertension (Table 2). In the age-and sex-matched normative population, the mean age at completion of the baseline survey was 63.5 years. Almost two thirds (65%) of respondents reported one or more comorbid conditions, the most common again being hypertension, back pain and arthritis (Table 2).

A comparison between survivors who completed one or both questionnaires indicated that those who completed both questionnaires had a significantly longer mean time since diagnosis at time of first enrollment (4.2 *versus* 5.1 years, p<0.001) and more often had a high educational level (19% *versus* 25%, p=0.013). No differences were observed between these groups for EORTC QLQ-C30 – Fatigue ($\overline{X}$ =28.6 *versus* $\overline{X}$ =28.3, p=0.88) or FAS Fatigue ($\overline{X}$ =21.9 *versus* $\overline{X}$ =21.4, p=0.33) scores.

Table 1. Socio-demographic and clinical characteristics of questionnaire respondents, non-respondents, and patients with unverifiable addresses.

	Respondents N=824	Non-respondents N=212	Patients with unverifiable addresses N=184	
	N(%)	N(%)	N(%)	p-value
Sex				0.02[1]
Male	509 (62)	128 (61)	94 (51)	
Female	315 (38)	84 (39)	90 (49)	
Age at time of survey: mean (SD)	63.5 (12.4)	62.4 (14.0)	60.3 (14.8)	0.02[1]
<55 years	189 (23)	58 (27)	62 (34)	
55-69 years	336 (41)	75 (35)	59 (32)	
70+ years	299 (36)	79 (37)	63 (34)	
Years since diagnosis: mean (SD)	4.2 (2.7)	4.3 (2.9)	5.1 (2.9)	0.12
0-1 years	168 (20)	64 (30)	32 (17)	
2-4 years	316 (38)	70 (33)	65 (35)	
5-7 years	210 (25)	44 (21)	50 (27)	
8-10 years	130 (16)	34 (16)	37 (20)	
Stage at diagnosis				0.01[2]
I	202 (25)	41 (19)	48 (26)	
II	127 (15)	33 (16)	20 (11)	
III	116 (14)	23 (11)	19 (10)	
IV	202 (25)	44 (21)	51 (28)	
Unknown[#]	177 (21)	71 (33)	46 (25)	
Grade				0.04[2]
Indolent	443 (54)	134 (63)	106 (56)	
Aggressive	381 (46)	78 (37)	78 (44)	
Primary treatment				0.05
Radiotherapy	75 (9)	21 (10)	21 (11)	
Chemotherapy	345 (42)	65 (31)	63 (34)	
RT+CH*	99 (12)	29 (14)	21 (11)	
Active surveillance[+]	224 (27)	76 (36)	63 (34)	
CH+/-RT+Transplant*	11 (1)	6 (3)	0 (0)	
S+/-RT+/-CH*	70 (9)	14 (7)	16 (9)	

Note. [1]p-value reflects differences between respondents and patients with unverifiable addresses. [2]p-value reflects differences between respondents and non-respondents. [#]Tumor stage could not be determined in some subtypes of indolent non-Hodgkin Lymphoma. *RT= radiotherapy, CH= chemotherapy, Transplant= autologous stem cell or bone marrow transplantation, S= surgery, +/- = with or without. [+] Patients are under active surveillance and receive no therapy.

Table 2. Socio-demographic characteristics of NHL survivors (N=824), and respondents of an age- and sex-matched normative population (N=602).

	NHL survivors N=824	Norm population N=602
	N (%)	N (%)
Sex		
Male	509 (62)	400 (66)
Female	315 (38)	202 (34)
Age at time of survey: mean (SD)	63.5 (12.4)	63.5 (13.2)
<55 years	189 (23)	144 (24)
55-69 years	336 (41)	242 (40)
70+ years	299 (36)	216 (36)
Self-reported comorbidity		
No comorbid condition	215 (26)	214 (36)
1 comorbid condition	245 (30)	166 (28)
2 comorbid conditions	155 (19)	112 (19)
>2 comorbid conditions	148 (18)	108 (18)
Most frequent comorbid conditions		
Arthritis	183 (22)	125 (21)
Back pain	177 (21)	178 (30)
Hypertension	164 (20)	173 (29)
Marital status		
Partner	646 (78)	460 (76)
Alone	41 (5)	142 (24)
Divorced	41 (5)	Unknown
Widowed	80 (10)	Unknown
Education level[$]		
Low	139 (17)	36 (6)
Medium	485 (59)	338 (56)
High	179 (22)	224 (37)

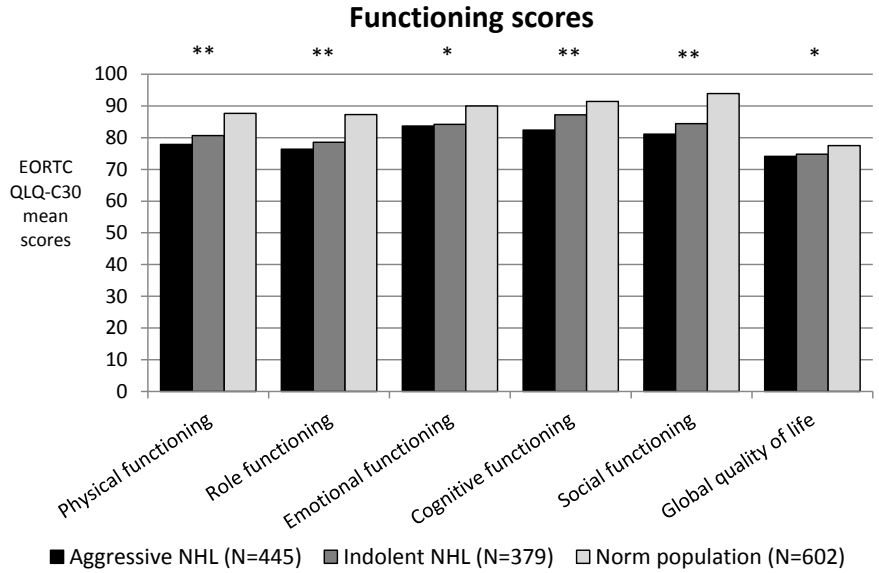
Note. NHL=Non-Hodgkin Lymphoma; [$]Education levels included low= no/primary school; medium= lower general secondary education/vocational training; or high= pre-university education/ high vocational training/university

Health-related quality of life and fatigue among survivors of non-Hodgkin's lymphoma and the normative population

Compared to an age- and sex-matched normative population, responding NHL survivors had, on average, worse scores for the EORTC QLQ-C30 Physical, Role, Cognitive and Social Functioning domains. NHL survivors also reported more Fatigue, Dyspnea, Sleeping Problems, Appetite Loss, Diarrhea and Financial Problems (all p≤0.001 and clinically relevant; Figure 1A and 1B). Scores between survivors of indolent and aggressive NHL were not significantly different. No clinically significant differences were found in EORTC QLQ-C30 mean fatigue scores depending on years since diagnosis (Figure 2).

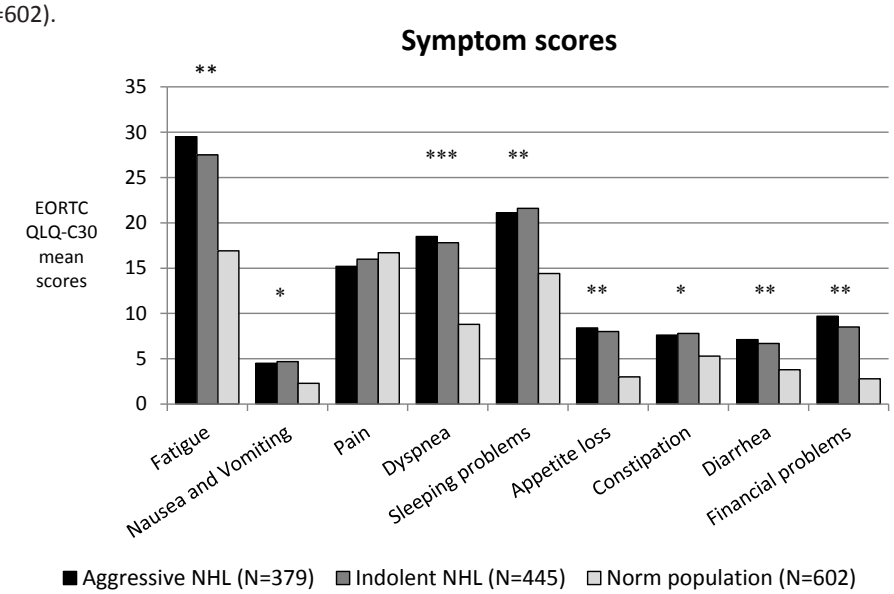
Thirty-nine percent (n=321) of the NHL survivors did not have clinically relevant worse scores, i.e. they had a ≤5 point difference, for the EORTC QLQ-C30 Fatigue scale than the normative population. The other 61% did have clinically relevant worse scores for Fatigue, with the difference being small (>5 to 13 point difference) in 17% (n=140) of survivors; medium (>13 to 19 point difference) in 15% (n=124) and large (>13 point difference) in 29% (n=239).

Figure 1a. Differences on EORTC QLQ-C30 mean functioning and global quality of life scores between aggressive NHL survivors (N=445), indolent NHL survivors (N=379) and an age- and sex-matched normative population (N=602).



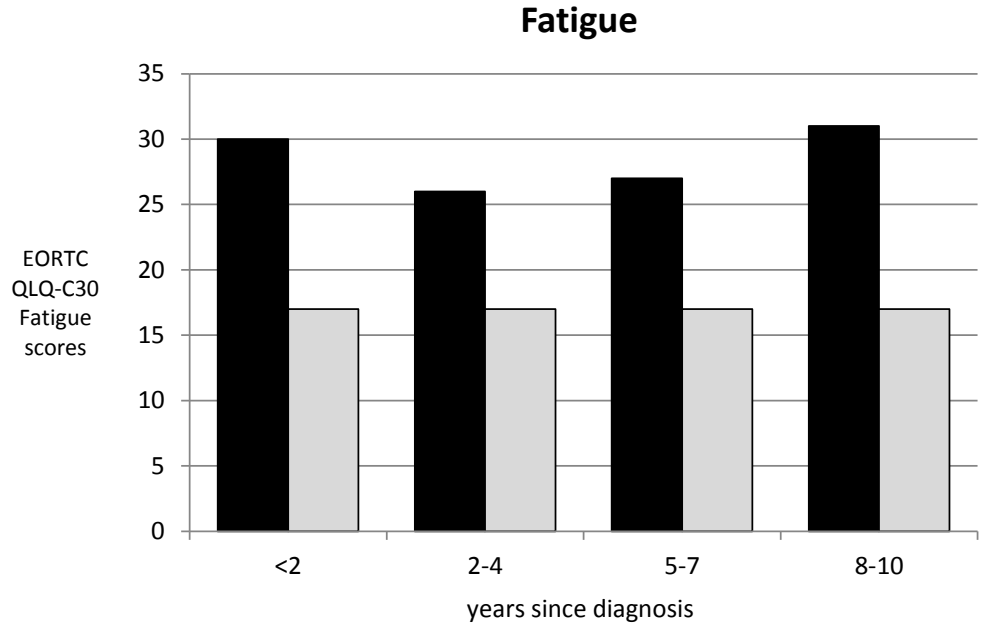
Note.*p<0.001; **p<0.001 and small clinically important differences[30]. A higher score implies a better HRQoL.

Figure 1b. Differences on EORTC QLQ-C30 mean symptom scores between aggressive NHL survivors (N=379), indolent NHL survivors (N=445) and an age- and sex-matched normative population (N=602).



Note. *p<0.001; **p<0.001 and small clinically important differences[30]; ***p<0.001 and medium clinically important differences[30]. A higher score refers to more symptoms.

Figure 2. Differences between EORTC QLQ-C30 fatigue scores of all NHL survivors (N=824) according to survival years since diagnosis and an age- and sex-matched normative population (N=602).



Note. All p<0.001 and small or medium clinically important differences[30]. A higher score refers to more fatigue.

Fatigue over time

The 1-year follow-up questionnaire was completed by 434 NHL survivors and 514 respondents of the normative population. With respect to FAS Fatigue (NHL survivors only), mean scores remained significantly stable over time – (T1: $\bar{X}$=21; T2: $\bar{X}$=22, Table 3). However, 22% reported deteriorated fatigue scores with a mean difference of 6.4 and 19% reported improved scores with a mean difference of 5.9. With respect to the EORTC QLQ-C30 Fatigue, mean scores also remained significantly stable over time – (T1: $\bar{X}$=28; T2: $\bar{X}$=29, Table 3), 32% reported deteriorated scores with a mean difference of 21 points, and 31% showed improved scores with a mean difference of 19 points. Similar mean scores and percentages of deterioration and improvement were observed when focusing on diffuse large B-cell lymphoma or follicular lymphoma only (Table 3). Mean scores of the normative population – changed slightly over time (T1: $\bar{X}$=17; T2: $\bar{X}$=18, p<0.04; Table 2) with 31% reporting deteriorated and 24% reporting improved EORTC QLQ-C30 Fatigue scores.

Of NHL survivors, 54% reported constant EORTC QLQ-C30 Fatigue, i.e. had a Fatigue score above 22 for both T1 and T2. Of respondents of the normative population, 30% reported constant EORTC QLQ-C30 Fatigue. With respect to FAS Fatigue, 40% of NHL survivors reported constant fatigue i.e. had a Fatigue score above 21 on both T1 and T2.

Table 3. Fatigue mean scores (SD) at baseline (T1) and follow-up (T2) among NHL survivors and respondents of the norm population who completed two questionnaires (N=434 NHL survivors; N=515 norm population), and percentages of patients/respondents who deteriorated/ improved between these time points (mean difference and SD).

	Baseline (T1)	**Follow-up (T2)**		**Deteriorated**		**Improved**	
	Mean (SD)	Mean (SD)	p-value	%	Mean difference (SD)	%	Mean difference (SD)
FAS Fatigue NHL survivors in total (n=434)	21 (7.6)	22 (7.6)	0.18	22%	6.4 (2.7)	19%	5.9 (2.3)
FAS Fatigue Large B cell NHL survivors (n=132)	22 (7.2)	22 (7.6)	0.93	19%	7.0 (3.6)	22%	5.8 (1.6)
FAS Fatigue Follicular NHL survivors (n=82)	22 (8.2)	22 (7.6)	0.50	22%	6.4 (2.7)	17%	6.7 (4.3)
EORTC Fatigue NHL survivors in total (n=434)	28 (26)	29 (26)	0.42	32%	21 (13)	31%	19 (11)
EORTC Fatigue Large B cell NHL survivors (n=132)	29 (26)	28 (25)	0.81	33%	21 (13)	13%	22 (13)
EORTC Fatigue Follicular NHL survivors (n=82)	28 (25)	27 (24)	0.79	32%	19 (9.3)	35%	18 (8.1)
EORTC Fatigue Norm population	17 (19)	18 (21)	0.04	31%	20 (12)	24%	19 (10)

Note. Deterioration and improvement where determined using the guideline of at least a clinically small difference with respect to the EORTC[30] (deterioration >5 point difference; improvement >4 point difference) and Norman's rule of thumb for the FAS[32] (half SD, i.e.3.8 for both deterioration and improvement).

Associations with fatigue

Multivariate logistic regression analyses showed that NHL survivors who reported constant fatigue (on both EORTC QLQ-C30 and FAS) were more often diagnosed with stage IV disease and more often reported comorbid diseases. They were additionally more often female and divorced (Table 4). Survivors who remained fatigued (however only on FAS fatigue) were also more often diagnosed longer ago, were under active surveillance and had a lower educational level.
With respect to survivors of diffuse large B-cell and follicular lymphoma, survivors who reported constant fatigue (on both the EORTC QLQ-C30 and FAS) reported comorbid diseases more often. Survivors of follicular lymphoma who reported constant fatigue were also more often females; however, this was only found on the FAS (Table 4).
Respondents of the normative population who reported constant fatigue also reported comorbid diseases more often and more often had no partner (Table 4).

DISCUSSION

The majority of NHL survivors showed a constant, high level of fatigue in this population-based study up to 10 years after diagnosis. Six out of 10 survivors reported clinically relevant worse fatigue scores compared to the normative population. HRQoL was also worse to a clinically relevant degree among survivors. Mean fatigue scores remained significantly stable over time; 22–28% reported clinically relevant deterioration, whereas 19–23% reported clinically relevant improvement; 44–54% reported constant fatigue. No clinically significant differences in EORTC QLQ-C30 mean fatigue scores were observed in relation to years since diagnosis.

Changes over time in NHL survivors have so far been investigated in three small studies, only including short-term survivors for a maximum of 18 months after primary treatment. One prospective study found no clinically significant change in mean EORTC QLQ-C30 Fatigue scores[16]. One Dutch study and another Norwegian study showed mean deteriorations in EORTC QLQ-C30 Fatigue scores of 14 and 10 points when comparing start of treatment scores with those at 18 months and 1 year of follow up, respectively[14,15]. A limitation of these studies is that they all focused on mean differences. Mean scores do not reflect individual changes. Given the large standard deviations, there must be high degrees of variations within these groups. A better way is, therefore, to make a distinction between patients who improved and patients who deteriorated.

The present study showed that survivors with stage IV disease and comorbid conditions more often reported constant fatigue. Females and divorced survivors were also more likely to remain fatigued. In the normative population, we also observed a relation between comorbidity and having a partner and fatigue. This relation is not, therefore, specific to NHL survivors but is probably applicable to people in general. Type of NHL (aggressive or indolent), treatment, and survival time since diagnosis were not associated, or only associated with one measure of fatigue in NHL survivors. The ECR collects data on primary treatment only. More detailed treatment information, longitudinally assessed, will enable us to study the relation between initial treatment and HRQoL and fatigue in more detail. Furthermore, detailed information about

Table 4. Odds ratios with confidence intervals (CI) of the multivariate logistic regression model evaluating independent variables for EORTC QLQ-C30 and FAS Fatigue scores for patients (N=434) and respondents of the normative population (N=515) who completed two questionnaires and remained fatigued.

Independent variable	FAS Fatigue			EORTC Fatigue			
	All NHL survivors	Large B-cell NHL	Follicular NHL	All NHL survivors	Large B-cell NHL	Follicular NHL	Norm population
	Odds ratio (CI)	Odds ratio (CI)	Odds ratio (CI)	Odds ratio (CI)	Odds ratio (CI)	Odds ratio (CI)	Odds ratio (CI)
Age (time of questionnaire)	ns	ns	ns	ns	ns	ns	ns
Sex (women)	1.6 (1.0-2.5)*	ns	3.4 (1.3-8.7)*	1.6 (1.0-2.5)*	ns	ns	ns
Time since diagnosis	1.1 (1.0-1.2)*	ns	ns	ns	ns	ns	NA
Tumor stage:							NA
Stage 1 (reference)	-	-	-	-	-	-	NA
Stage 2	ns	ns	ns	ns	ns	ns	NA
Stage 3	ns	ns	ns	ns	ns	ns	NA
Stage 4	2.3 (1.0-5.2)*	ns	ns	2.7 (1.2-5.8)*	ns	ns	NA
Aggressive tumor grade	ns	NA	NA	ns	NA	NA	NA
Radiotherapy (yes)	ns	ns	ns	ns	ns	ns	NA
Chemotherapy (yes)	ns	ns	ns	ns	ns	ns	NA
Active surveillance (yes)	2.9 (1.0-8.1)*	ns	ns	ns	ns	ns	NA
Comorbidity:							
None (reference)	-	-	-	-	-	-	-
1	2.7 (1.4-5.1)*	ns	ns	1.8 (1.0-3.2)*	2.9 (1.1-8.0)*	ns	2.0 (1.1-3.7)*
2	3.9 (1.9-8.3)*	ns	10.2 (2.2-47.1)*	ns	ns	6.5 (1.3-33.9)*	4.3 (2.2-8.2)*
>2	7.2 (3.3-15.7)*	6.3 (1.7-23.8)*	26.8 (5.3-135.7)*	4.7 (2.2-10.1)*	7.2 (1.9-27.6)*	13.9 (2.3-82.9)*	16.1 (7.9-32.9)*
Marital status:							
Partner (reference)	-	-	-	-	-		NA
Divorced	6.0 (1.9-18.7)*	ns	ns	3.5 (1.1-11.1)*	ns	ns	NA
Widowed	ns	ns	ns	ns	ns	ns	NA
Alone	ns	ns	ns	ns	ns	ns	NA
Marital status:							
Partner (reference)	-	-	-	-	-	-	-
No partner	ns	ns	ns	ns	ns	ns	2.7 (1.6-4.6)*
Educational level:							
Low	2.2 (1.1-4.5)*	ns	ns	ns	ns	ns	ns
Middle (reference)	-	-	-	-	-	-	-
High	ns	ns	ns	ns	ns	ns	ns

Note. *p<0.05; CI=confidence interval; ns= not significant, NA= Not Applicable.

disease progression could also contribute to unraveling the course of HRQoL and fatigue and will help health care providers to give their patients better information about their expected HRQoL. As our HRQoL study is embedded in PHAROS (Population based HAematological Registry for Observational Studies) in which more detailed disease and treatment information is collected, as well as long-term side effects, we will be able to determine this relation better in the near future.

NHL survivors reported worse HRQoL compared to that of an age- and sex-matched normative population. Clinically relevant worse scores for survivors were observed for fatigue, appetite loss, diarrhea, dyspnea and all function scales including financial problems. One prospective and three cross-sectional studies also observed clinically worse scores for HRQoL domains for NHL survivors compared with those of a normative population[13, 15, 17, 20].

Numerous patients in our study showed large improvements (19–23%) or deteriorations (22–28%) within 1 year, which both indicate a clinically relevant change[31]. However, it is too soon to determine whether this can be defined as an actual change, due to regression to the mean. A longer follow-up time is needed to identify whether these differences can be considered as real changes or fluctuations over time.

Significant differences were not observed between patients with indolent or aggressive NHL, recapitulating findings in an American cross-sectional study[33] nor between short- or long-term survivors, confirming results of a cross-sectional study among 761 NHL survivors[20]. This suggests that there is no improvement in time, which is also shown by our 1-year follow-up results.

Prevalence rates for cancer-related fatigue vary widely. Percentages between 32% and 60% have been reported[34-36] and in a recently published study an overall prevalence of 48% was found[37]. The observed percentage of 61% in this study is somewhat higher. In our study, 29% of survivors reported large, clinically important fatigue, whereas 15% reported medium clinically important fatigue, making a total of 44%. Adding the survivors with small, clinically important fatigue produced the observed total of 61% of patients with cancer-related fatigue. Besides differences between types of cancer, the use of different cut-off scores and fatigue assessment instruments contribute to the differences in reported prevalence[38-40].

The underlying mechanisms that cause constant cancer-related fatigue are not yet clear[41]. Many factors are associated with the development of fatigue, such as type of treatment, the disease itself, medication-related adverse events, biological modifiers (such as interferon), depression, physical inactivity, anxiety, pain and sleep disturbances[42-46]. Although the cause of fatigue is not completely clear, results of a recently published review[47] show that patients with fatigue may benefit from pharmacological and/or non-pharmacological treatments, such as cognitive-behavioral interventions and exercise[48]. Further research is necessary to determine whether an early intervention for fatigue can reduce this long-term complication and whether patients can benefit from late intervention.

The present study had the following limitations: although information was available concerning socio-demographic and clinical characteristics of the non-respondents and patients with

unverifiable addresses, it remains unknown whether non-respondents declined to participate in the study because of poor health or the absence of symptoms. Comparing patients who completed one questionnaire with patients who completed two questionnaires only indicated differences in mean time since diagnosis and educational level. This perhaps resulted in a small selection bias. In addition, there is always an uncertainty with the reproducibility of self-reported questionnaires. Some of the changes might be ascribed to that arbitrariness. The strengths of our study are the population-based sampling frame instead of a hospital-based sampling frame. Furthermore, the large range in elapsed time since diagnosis facilitates extrapolation of the results to a broad range of NHL survivors in the population. In addition, the longitudinal design provides important information about development over time.

In conclusion, six out of every ten NHL survivors reported a high level of fatigue up until 10 years after diagnosis. HRQoL and fatigue scores of survivors were clinically relevant and worse than those of an age- and sex-matched normative population. Fatigue mean scores remained significantly stable over time and 44–54% of survivors reported constant fatigue. Survivors with stage IV disease, comorbid conditions as well as females and divorced survivors were more likely to remain fatigued. Having comorbidities and being without a partner were also associated with continuous fatigue in the normative population. As research on the underlying determinants of fatigue proceeds, health care providers should continue to screen patients on their level of fatigue and inform them about possible rehabilitation programs.

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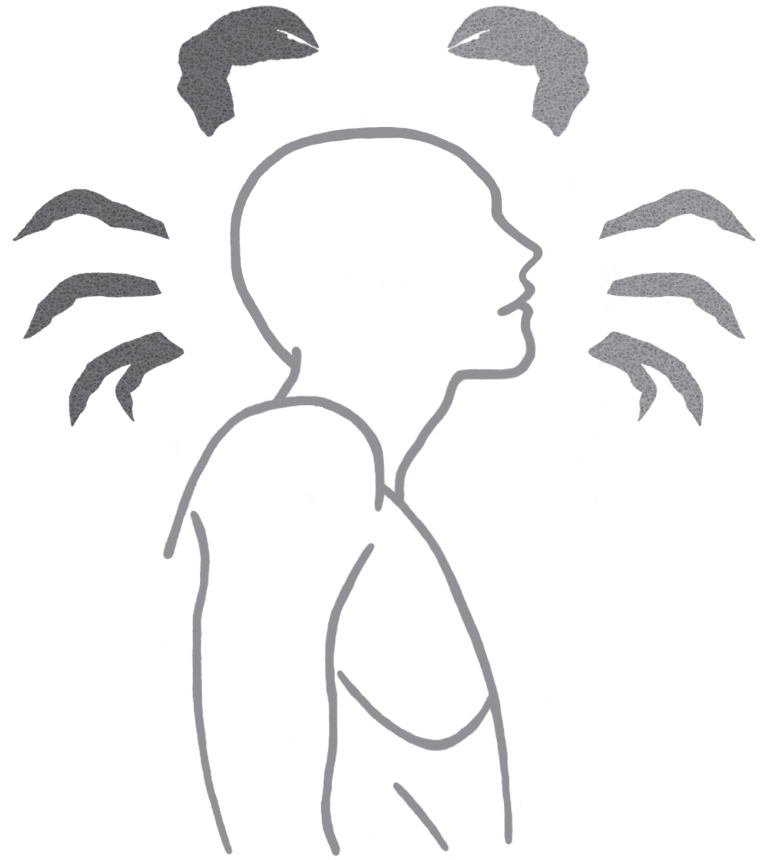
CHAPTER 8

Perceived information provision and satisfaction among lymphoma and multiple myeloma survivors - results from a Dutch population-based study



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ABSTRACT

To improve post treatment care for (long-term) lymphoma survivors in the Netherlands, survivorship clinics are being developed. As information provision is an important aspect of survivorship care, our aim was to evaluate the current perceived level of and satisfaction with information received by non-Hodgkin's lymphoma (NHL), Hodgkin's lymphoma (HL) and multiple myeloma (MM) survivors, and to identify associations with socio-demographic and clinical characteristics. The population-based Eindhoven Cancer Registry was used to select all patients diagnosed with NHL, HL and MM from 1999 to 2009. In total, 1,448 survivors received a questionnaire and 1,135 of them responded (78.4%). The EORTC QLQ-INFO25 was used to evaluate the perceived level of and satisfaction with information. Two thirds of survivors were satisfied with the amount of received information, with HL survivors being most satisfied (74%). At least 25% of survivors wanted more information. Young age, having had chemotherapy, having been diagnosed more recently, using internet for information, and having no comorbidities were the most important factors associated with higher perceived levels of information provision. Although information provision and satisfaction with information seems relatively good in lymphoma and MM survivors, one-third expressed unmet needs. Furthermore, variations between subgroups were observed. Good information provision is known to be associated with better quality of life. Survivorship care plans could be a way to achieve this.

INTRODUCTION

On January 1, 2009 there were approximately 21,000 non-Hodgkin lymphoma (NHL), 5,300 Hodgkin lymphoma (HL), and 3,300 multiple myeloma (MM) survivors in the Netherlands[1]. These numbers are expected to increase to approximately 32,000 NHL, 6,300 HL and 4,300 MM survivors by 2020[1]. This substantial raise will result in an increasing health care burden in haematology, especially indolent lymphomas and MM, which both are characterised by a prolonged clinical course with repeated relapses and slow but on-going progression[2].

To improve care for this growing group of cancer survivors, a nationwide initiative of haematologists, radiation oncologists, epidemiologists and internists has founded a Working Group named 'BETTER' ('BETER' in Dutch), which is currently developing protocols for standardized long-term care for HL and NHL survivors and establishing survivorship clinics. The goals of these clinics are to minimize the occurrence and influence of late effects and to improve survivors' quality of life (QoL) by: informing survivors about long-term risks, advice preventive measures, suggest screening and improve aftercare by providing rehabilitation programs[3].

Patient information is an essential component of cancer care and rehabilitation[4]. Patients, who are well-informed about their cancer, treatment, and aftercare, are more likely to complete their therapy and are less anxious thereafter[5, 6]. Providing adequate information to cancer patients can reduce the psychological burden and improve patients QoL and their satisfaction with care[7, 8]. This is important since lymphoma and MM survivors report lower QoL compared to normative populations even years after diagnosis[9, 10].

Up to now, no studies have investigated the perceived level of and satisfaction with information provision in NHL, HL and MM survivors. If factors associated with information satisfaction are known, health care providers can better give adequate information to those who need it, which can contribute to an improved quality of care and QoL. The aim of the present study was therefore to measure the perceived level of, and satisfaction with information received by survivors of indolent NHL (I-NHL), aggressive NHL (A-NHL), HL and MM, and to identify associations with socio-demographic and clinical characteristics for each tumour type.

METHODS

Setting and population

This study is part of a dynamic longitudinal population-based survey among lymphoma and MM survivors registered within the Eindhoven Cancer Registry (ECR) of the Comprehensive Cancer Centre South (CCCS) and is embedded in PHAROS (Population based HAematological Registry for Observational Studies). The ECR records data on all patients who are newly diagnosed with cancer in the southern part of the Netherlands, an area with 2.3 million inhabitants, 18 hospital locations and 2 large radiotherapy institutes. The ECR was used to select all patients who were diagnosed with NHL, HL and MM between January 1st 1999 and January 1st 2009. We included

all subtypes of indolent (including Chronic Lymphocytic Leukaemia-like) and aggressive B-cell NHL, HL, and MM as defined by the International Classification of Diseases for Oncology-3 codes (ICD-O-3)[11].
Deceased patients were excluded by linking the ECR database with the Central Bureau for Genealogy. Ethical approval for the study was obtained from a regional, certified Medical Ethics Committee.

Data collection
Data collection took place in 2009 and was done within PROFILES (Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship). PROFILES is a registry for the study of the physical and psychosocial impact of cancer and its treatment from a dynamic, growing population-based cohort of both short and long-term cancer survivors. PROFILES contains a large web-based component and is linked directly to clinical data from ECR. Details of the data collection method have been previously described[12]. Data from the PROFILES registry will become available for non-commercial scientific research, subject to study question, privacy and confidentiality restrictions, and registration (www.profilesregistry.nl).
In May 2009, patients between 1 and 10 years after diagnosis where included in the study and received the first questionnaire. In November 2009, patients diagnosed between May and November 2009 were invited to participate.

Study measures
The Dutch version of the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-INFO25 questionnaire was used to evaluate the perceived level of and satisfaction with information among NHL, HL and MM patients[13]. This 25-item questionnaire incorporates four information provision subscales: perceived receipt of information about the disease; medical tests; treatment and other care services. Additionally, it contains several single items on receiving written information or information on CD or tape/video and items on the satisfaction with and helpfulness of the received information. Answer categories range from one (not at all) to four (very much), except for four items which have a two point scale. Furthermore, an open question is asked on what topics survivors would like to receive more information on. After linear transformation, all scales and items range in scores from 0 to 100, with higher scores indicating better perceived information provision. The questionnaire has been internationally validated; and internal consistency for all scales is good (α>0.70), as is test-retest reliability (interclass correlations >0.70)[14]. Our data revealed Cronbach's alphas of 0.75 (disease), 0.88 (medical test), 0.88 (treatment) and 0.82 (other services) for the four subscales respectively. In addition to the EORTC QLQ-INFO25, we asked patients two single questions about the use of internet for seeking additional information, which could be answered with either yes or no.
Comorbidity at time of survey was categorized according to the adapted Self-administered Comorbidity Questionnaire (SCQ)[15]. Questions on survivors' marital status and educational level were also added to the questionnaire. Clinical information was available from the ECR that routinely collects data on tumour characteristics, including date of diagnosis, histology, Ann Arbor stage (where appropriate)[16], primary treatment, and patients' background characteristics, including gender and date of birth.

Statistical analysis
All statistical analyses were performed using SPSS version 17.0 (Statistical Package for Social Sciences, Chicago, IL, USA) and P values of <0.05 were considered statistically significant. For the EORTC QLQ-INFO25 we used a score of ≥ 10 points difference on subscales to define a clinical important difference[17].
Differences in socio-demographic and clinical characteristics between respondents, non-respondents, and patients with unverifiable addresses and between tumour types were compared with a chi-square, t-test, or its non-parametric equivalent where appropriate.
Multi-item scales of the EORTC QLQ-INFO25 were included in the analyses if at least half of the items from the scale were answered, according to the EORTC QoL guidelines[13, 14, 18]. ANOVA and chi-square were performed to investigate mean differences between tumour type (independent variables) and the EORTC QLQ-INFO25 scales (dependent variables).
Multivariate regression analyses were performed to investigate the independent association of socio-demographic and clinical characteristics with the subscales of the EORTC QLQ-INFO25. All socio-demographic and clinical variables were included, this was determined a priori. Stage was only included in the analyses for A-NHL and HL, since it was not available for I-NHL and MM (Table 1).
Logistic regression analyses were performed with received information satisfaction as outcome measure; one for the total group and four for the tumour types. Therefore, patients were categorized into two groups: (a) patients who were unsatisfied or only a little satisfied, classified as unsatisfied and (b) patients who were quite satisfied or very satisfied, classified as satisfied. Again, all socio-demographic and clinical variables were included. Stage was only included in the analyses for A-NHL and HL, since stage was not available in I-NHL and MM.

RESULTS

Patient and tumour characteristics
Of the 1,448 lymphoma and MM survivors who were sent a questionnaire, 1,135 (78%) completed it. Non-respondents were more recently diagnosed and less often diagnosed with stage I disease. Furthermore, they were less often treated with chemotherapy compared to respondents. Patients with unverifiable addresses were younger, diagnosed longer ago, less often treated with chemotherapy and more often had active surveillance as primary treatment compared to respondents. There were no differences in response according to tumour type or gender (Table 1).
Participating HL survivors were significantly younger, more often had a job and reported fewer comorbid conditions than I-NHL, A-NHL and MM survivors. MM survivors were most recently diagnosed compared to the other three tumour groups (Table 2).

Satisfaction with and amount of information
Satisfied cancer survivors (n=724; 67%) perceived to have received more information (disease, medical tests, treatment and other services) and found the information more useful than dissatisfied patients (n=411; 33%), with mean differences ranging between 46 to 74 points (all p<0.01).

In total, 29% of survivors would have liked to receive more information (29% I-NHL, 25% A-NHL, 30% HL, 29% MM). Most frequently mentioned topics to receive more information about were cause and course of disease (45% I-NHL, 59% A-NHL, 24% HL, 54% MM), late effects of treatment (46% I-NHL, 37% A-NHL, 50% HL, 30% MM) and psychosocial aftercare (10% I-NHL, 23% A-NHL, 26% HL, 30% MM).

Table 1. Socio-demographic and clinical characteristics of questionnaire respondents, non-respondents and patients with unverifiable addresses.

	Respondents	**Non-respondents**	**Patients with unverifiable addresses**	
	N= 1,135	**N= 313**	**N= 271**	
	N (%)	N (%)	N (%)	p-value
Tumour type				0.06
I-NHL	443 (39)	140 (45)	110 (41)	
A-NHL	375 (33)	80 (26)	82 (30)	
HL	164 (14)	37 (12)	44 (16)	
MM	153 (14)	56 (23)	35 (13)	
Age (at time of survey) (mean ± SD)	61.6 (14)	60.5 (16)	57.2 (16)	<0.01
<55	312 (28)	104 (33)	113 (42)	
55-69	452 (40)	99 (32)	79 (29)	
≥70	369 (33)	110 (35)	79 (29)	
Years since diagnosis (mean ± SD)	3.7 (2.7)	3.2 (3.0)	3.9 (2.9)	<0.01
0-1	313 (28)	130 (42)	71 (26)	
2-4	422 (37)	92 (29)	102 (38)	
5-7	264 (23)	46 (15)	56 (21)	
8-10	136 (12)	45 (14)	42 (16)	
Gender				0.38
Male	677 (60)	184 (59)	147 (55)	
Female	457 (40)	127 (41)	120 (45)	
Stage at diagnosis				<0.01
I	248 (22)	52 (17)	65 (24)	
II	220 (19)	57 (18)	39 (14)	
III	183 (16)	40 (13)	42 (16)	
IV	218 (19)	50 (16)	58 (21)	
Unknown	266 (23)	114 (36)	67 (25)	
Primary treatment				
Radiotherapy	88 (7.8)	17 (5.4)	20 (7.4)	0.09
Chemotherapy	515 (45)	118 (38)	106 (39)	0.02
Chemotherapy + radiotherapy	239 (21)	56 (18)	52 (19)	0.11
Active surveillance[+]	233 (21)	89 (23)	71 (26)	<0.01
Stem cell transplantation	58 (5.1)	16 (5.1)	8 (3.0)	0.07

Note. I-NHL= indolent non-Hodgkin lymphoma, A-NHL= aggressive non-Hodgkin Lymphoma, HL= Hodgkin lymphoma, MM= multiple myeloma. [+] Patients are under active surveillance and receive no therapy.

Table 2. Socio-demographic and clinical characteristics of cancer survivors, stratified by tumour type.

	I-NHL N=443	**A-NHL N=375**	**HL N=164**	**MM N=153**	
	N (%)	N (%)	N (%)	N (%)	p-value
Age (at time of survey) (mean ± SD)	64.1 (11)	63.3 (14)	46.6 (15)	66.1 (10)	<0.01
<55	90 (20)	90 (24)	112 (69)	20 (13)	
55-69	199 (45)	136 (36)	38 (23)	79 (52)	
≥70	154 (35)	148 (40)	13 (8.0)	54 (35)	
Years since diagnosis (mean ± SD)	4.0 (2.7)	3.5 (2.6)	4.4 (2.9)	2.4 (2.3)	<0.01
0-1	100 (23)	108 (29)	36 (22)	69 (45)	
2-4	169 (38)	144 (38)	50 (31)	59 (39)	
5-7	113 (26)	85 (23)	49 (30)	17 (11)	
8-10	61 (14)	38 (10)	29 (18)	8 (5.2)	
Gender					0.10
Male	266 (60)	239 (64)	89 (54)	83 (55)	
Female	177 (40)	136 (36)	75 (46)	69 (45)	
Stage at diagnosis					<0.01
I	NA	118 (32)	30 (18)	NA	
II	NA	90 (24)	83 (51)	NA	
III	NA	68 (18)	33 (20)	NA	
IV	NA	93 (25)	17 (10)	NA	
Unknown	NA	6 (1.6)	1 (0.6)	NA	
Primary treatment					
Radiotherapy (only)	64 (14)	12 (3.2)	4 (2.4)	8 (5.2)	<0.01
Chemotherapy (only)	157 (35)	235 (63)	65 (40)	58 (38)	<0.01
Chemotherapy+ radiotherapy	14 (3.2)	98 (26)	94 (57)	33 (22)	<0.01
Active surveillance[+]	187 (42)	25 (6.7)	1 (0.6)	20 (13)	<0.01
Stem cell transplantation	8 (1.8)	22 (5.9)	0 (0)	28 (18)	<0.01
Comorbidity					<0.01
None	108 (26)	103 (30)	75 (48)	26 (19)	
1	122 (30)	118 (34)	46 (30)	43 (31)	
2	90 (22)	65 (19)	14 (9.0)	35 (26)	
3 or more	90 (22)	60 (17)	20 (13)	33 (24)	
Marital status					0.41
Partner	353 (81)	287 (79)	122 (75)	116 (77)	
No partner	84 (19)	77 (21)	41 (25)	35 (23)	
Education level[$]					0.11
Low	69 (16)	62 (17)	16 (9.8)	30 (20)	
Medium	264 (61)	219 (61)	99 (61)	95 (63)	
High	101 (23)	80 (22)	48 (29)	27 (18)	
Current occupation					<0.01
Employed	166 (46)	128 (45)	112 (84)	39 (34)	
Not working/retired	198 (54)	155 (55)	21 (16)	76 (66)	
Follow-up care					<0.01
No	42 (10)	32 (10)	12 (8)	30 (24)	
2-4 times a year	324 (80)	245 (74)	81 (52)	95 (75)	
Once a year	35 (9)	52 (16)	62 (40)	1 (1)	
Once every two years	3 (1)	2 (1)	1 (1)	0 (0)	

Note: I-NHL= indolent non-Hodgkin lymphoma, A-NHL= aggressive non-Hodgkin Lymphoma, HL= Hodgkin lymphoma, MM= multiple myeloma. [+]Patients are under active surveillance and receive no therapy. [$]Education levels included low = no/primary school; medium = lower general secondary education/vocational training; or high = pre-university education/ high vocational training/university. NA=Not Available.

Associations with perceived level of and satisfaction with information

Mean scores on perceived level of and satisfaction with information on all scales were the highest for HL survivors and the lowest for I-NHL survivors (Table 3). Furthermore, HL survivors found the information more useful compared to all other tumor groups.

Multivariate linear regression analyses including all patients in one model showed that receiving more disease-related information was associated with, having no comorbid conditions, using internet for information and hospital (β=0.11; p<0.01; Table 4). More information on medical tests was associated with less comorbidity, high education and use of internet. Furthermore, receiving more information about treatment and other services was associated with younger age, having had chemotherapy, less comorbidity, and hospital (β between 0.08 and 0.10; p<0.05). Being diagnosed with I-NHL and being under active surveillance was associated with a lower perceived level of receiving information about treatment. Satisfaction with information was independently associated with having had chemotherapy and negatively associated with comorbidity.

Additional multivariate analyses within the different tumour types showed similar findings (data not shown in table). Younger age (β between -0.13 and -0.46; p<0.05) and a more recent diagnosis (β between -0.10 and -0.20; p<0.05) were frequently positively associated with perceived information provision, whereas comorbidity (β between -0.13 and -0.23; p<0.05) was frequently negatively associated with perceived information provision.

I-NHL survivors with a low or medium educational level reported lower levels of treatment information (β=-0.15; p<0.05) compared to those who were highly educated. A-NHL survivors with stage II or III disease (β=0.22; p<0.01) or those who received chemotherapy (β=0.17; p<0.01) reported higher perceived levels of information compared to those who did not. HL survivors with a low educational level (β=0.23; p<0.05) and those using internet (β=-0.18; p<0.05) reported higher levels of perceived information. Lastly, MM survivors under active surveillance reported lower perceived levels of information about treatment (β=-0.45; p<0.05) compared to patients who were actively treated.

Table 3. Mean EORTC QLQ-INFO25 subscale scores (± SD) according to tumour type.

	I-NHL N=443	A-NHL N=375	HL N=164	MM N=153	
EORTC QLQ-INFO25	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	p-value
Information about disease	50 (22)	53 (20)	56 (16)	51 (22)	<0.05[a]
Information about medical tests	63 (22)	64 (23)	68 (21)	65 (23)	0.15
Information about treatment	41 (24)	50 (21)	57 (19)	47 (24)	<0.01[b]
Information about other services	16 (21)	25 (24)	27 (22)	22 (21)	<0.01[c]
Satisfaction with information	60 (28)	61 (26)	66 (25)	61 (28)	0.15
Usefulness of information	62 (25)	66 (24)	73 (21)	62 (25)	<0.01[d]
	% Yes	% Yes	% Yes	% Yes	
Want more information	29%	25%	30%	29%	0.48
Want less information	3%	3%	2%	1%	0.74

Note. EORTC-QLQ INFO25 scales 0-100: a higher scores reflect better perceived information received. I-NHL= indolent non-Hodgkin lymphoma, A-NHL= aggressive non-Hodgkin Lymphoma, HL= Hodgkin lymphoma, MM= multiple myeloma. [a]= between I-NHL and HL; [b]= between I-NHL and A-NHL, HL, MM; between HL and A-NHL, MM; [c]= between I-NHL and A-NHL, HL, MM; [d]= between HL and I-NHL, A-NHL, MM.

Table 4. Standardized betas of multivariate linear regression analyses evaluating the association of independent variables with the information provision subscales.

	Disease	Medical tests	Treatment	Other	Satisfaction with received information
	Beta	Beta	Beta	Beta	Odds ± 95%CI
Tumour type					
I-NHL	-0.07	-0.07	-0.12**	-0.09	0.89 (0.52-1.52)
A-NHL	-0.05	-0.07	-0.04	0.03	0.78 (0.48-1.28)
HL	Ref	Ref	Ref	Ref	Ref
MM	-0.05	0.02	-0.03	0.00	0.81 (0.43-1.56)
Age	-0.05	0.01	-0.12**	-0.11**	1.00 (0.99-1.01)
Years since diagnosis	-0.01	0.01	0.02	-0.05	0.97 (0.92-1.03)
Gender					
Male	Ref	Ref	Ref	Ref	Ref
Female	0.01	0.02	-0.01	-0.01	0.77 (0.58-1.03)
Chemotherapy					
No	Ref	Ref	Ref	Ref	Ref
Yes	0.03	-0.01	0.14*	0.14**	1.81 (1.04-3.13)*
Radiotherapy					
No	Ref	Ref	Ref	Ref	Ref
Yes	-0.08	-0.06	-0.06	-0.07	1.00 (0.68-1.45)
Active surveillance					
No	Ref	Ref	Ref	Ref	Ref
Yes	-0.09	-0.08	-0.16**	-0.06	1.39 (0.76-2.55)
Stem cell transplantation					
No	Ref	Ref	Ref	Ref	Ref
Yes	0.07	0.06	0.05	0.06	1.51 (0.73-3.13)
Comorbidity					
None	Ref	Ref	Ref	Ref	Ref
1	-0.07	-0.04	-0.07	-0.02	0.74 (0.51-1.52)
2	-0.07	-0.05	-0.14**	-0.03	0.55 (0.36-0.85)**
3 or more	-0.90*	-0.90*	-0.07*	-0.01	0.55 (0.36-0.84)**
Marital status					
Partner	Ref	Ref	Ref	Ref	Ref
No partner	0.01	0.02	-0.02	0.00	1.21 (0.84-1.73)
Educational level[$]					
Low	0.02	-0.04	-0.02	-0.03	0.85 (0.52-1.38)
Medium	-0.03	-0.08*	-0.06	-0.05	0.81 (0.57-1.16)
High	Ref	Ref	Ref	Ref	Ref
Use of internet					
Yes	Ref	Ref	Ref	Ref	Ref
No	-0.08*	-0.07*	-0.04	-0.03	0.97 (0.71-1.32)

Note. *p<0.05; **p<0.01. I-NHL= indolent non-Hodgkin lymphoma, A-NHL= aggressive non-Hodgkin Lymphoma, HL= Hodgkin lymphoma, MM= multiple myeloma. [$]Education levels included low= no/primary school; medium= lower general secondary education/vocational training; or high= pre-university education/ high vocational training/ university.

DISCUSSION

In the present study among 1,135 NHL, HL and MM survivors, two-thirds of survivors were satisfied with the amount of received information about their haematological malignancy, respectively 65% of I-NHL, 67% of A-NHL, 74% of HL and 68% of MM survivors. However, variations were observed and at least a quarter of survivors wanted more information, with large differences between hospitals (range 24-40%).

Younger age, having had chemotherapy, using internet for information and having no comorbid conditions appeared to be the most important factors associated with higher perceived levels of information provision. Analyses per tumour type showed similar findings. Worth mentioning is that in the analyses per tumour, I-NHL, A-NHL and MM survivors who had been diagnosed more recently had higher perceived levels of information provision, which possibly indicates that information provision has improved with time. However, it is also possible that recall bias influenced these findings, for those diagnosed more recently the information received is still fresh in their memory and by the more frequent contacts with their physician in the phase more closely to diagnosis.

Our findings that the perceived level of information provision is associated with age, education, time since diagnosis, and disease stage are in line with other studies[19-24]. Studies have shown that older and lower educated patients tend to ask fewer questions during their visit with their physician, and might therefore receive less information[25, 26]. Furthermore, older patients have been found to take a more passive role in interaction with their physician and have a greater reliance that their physician will provide all information[24]. In addition, higher educated patients are more likely to seek information from other sources such as the internet and consequently obtain more information[24].
The results of our study, with 67% of survivors being satisfied with the amount of information received, were different compared to a study among mostly early stage melanoma survivors in which only 39% of survivors indicated to be satisfied[22]. These differences might be explained by the more chronic level and intense treatment of lymphoma and MM compared to early stage melanoma. In addition, lymphoma and MM survivors will have more visits with the physician and therefore a possible improved information provision. Patients' satisfaction is also influenced by patients' expectations of the course of their disease[27]. Patients expectations can vary widely, depending of the type of tumour[27]. HL survivors may be more satisfied with and score better on perceived information since they have a better prognosis compared to NHL and MM survivors.

Survivors who were satisfied with the received information scored significantly and clinically relevant higher on all information provision subscales and on the usefulness of information scale compared to the unsatisfied survivors. To improve information provision in the group of unsatisfied survivors, physicians could screen their patients by asking if they are satisfied with the amount of information received, and when unsatisfied, physicians can ask what the patients' information needs are.

To provide the needed (written) information to patients, physicians should think of the educational level of the information provision. Patients with a lower educational level and patients with a low level of literacy will need extra help to understand the information. In the US, more attention is being paid to health literacy[20, 21, 28], i.e. 'the degree to which individuals have the capacity to obtain, process and understand basic health information and services needed to make appropriate health decisions'[29], than in the Netherlands. Since our and other studies have observed that lower educated survivors report worse scores, more attention should be paid to providing information on a basic comprehensive level[19, 22, 23].

One-third of survivors would have liked to receive more information. The topic that was mentioned most often was information on late effects (37-50%) followed by information on the cause and course of the disease (24-59%) and psychosocial aftercare (10-26%). Inviting survivors for the 'BETTER' initiative could be an efficient solution to address these lasting information needs and leads to improved health care perception.

The present study has a few limitations. Although information was present concerning demographic and clinical characteristics of the non-respondents and patients with unverifiable addresses, it remains unknown why non-respondents declined to participate in the study. In addition, the cross-sectional design of our study limits the determination of causal associations between the study variables. Furthermore, the mean time since diagnosis was 3.7 years, which could influence the recall effect of information received. However, in the case of indolent lymphoma and MM patients who visit their physicians more often, this may not have been a major problem as the majority of those patients (95%) was still under active follow-up.
The strengths of our study are the population-based sampling frame instead of a hospital based sampling frame, the high response rate, and the large range in elapsed time since diagnosis. This facilitates to extrapolate the results to a broad range of lymphoma and MM survivors.

In conclusion, although information provision and satisfaction with information is relatively good in lymphoma and MM survivors, one third of the survivors were not satisfied with the perceived information provision and variations between subgroups of patients were observed. The differences found between the participating hospitals with an assumed similar patient population suggests that their remains room for improvement. As survival of NHL, HL and MM has improved over the past decades and the numbers of long-term survivors' increases, late effects of therapy become more important. Optimal, tailor-made and repeated information provision will lead to improved patient satisfaction and QoL. Implementation of survivorship care plans could contribute to the improvement of information provision[30].

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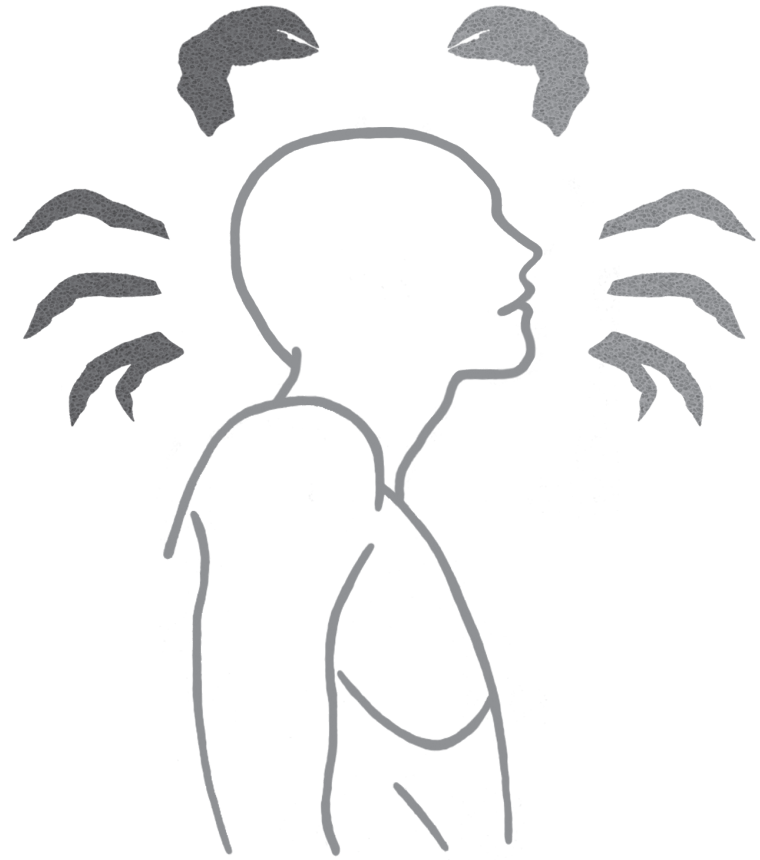
CHAPTER 9

Assessing the impact of cancer among Dutch non-Hodgkin lymphoma survivors compared with their American counterparts: A cross-national study



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ABSTRACT

Purpose

To understand cultural differences in the impact of cancer (IOC), by (1) performing an independent psychometric evaluation of the Dutch version of the Impact of Cancer Scale version 2 (IOCv2) in a non-Hodgkin lymphoma (NHL) sample and (2) examining differences between Dutch and American NHL survivors in perceived IOC and identifying associations with socio-demographic and clinical characteristics.

Methods

Data collected from 491 Dutch and 738 American NHL survivors were used in this study. IOCv2 responses were obtained from all survivors; the Dutch survivors also completed the European Organisation for Research and Treatment of Cancer Quality of Life Core questionnaire, which measures quality of life.

Results

Exploratory factor analysis of the Dutch version yielded a factor solution similar to the American structure but with some subscales merging into single factors. Internal consistency was good; Cronbach's alpha was 0.88 for the Positive and 0.94 for the Negative summary scales. Large differences were observed between survivors, whereby Dutch survivors reported fewer Positive (Δ-0.4, p<0.001, effect size: 0.27) and more Negative (Δ0.2, p≤0.001, effect size: 0.13) impacts of cancer independent of socio-demographic and clinical characteristics.

Conclusion

Similar impact domains of the IOCv2 were observed in the Dutch sample, providing evidence that IOCv2 scales measure common and important survivor concerns across two different Western nations. Higher positive impacts for US survivors might be explained by more personal control and availability of supportive services. Future research should focus on determinants of the impact of cancer in both Dutch and American survivors to gain better understanding of the factors that might improve it and suggest how health care may be modified toward that end.

INTRODUCTION

Advances in cancer treatment have led to an expansion in the number of cancer survivors in developed countries. Non-Hodgkin's lymphoma (NHL) is one of the diseases that has benefited from such advances. For both the Netherlands and the United States (US), the annual age-adjusted incidence of NHL is 1 in 5,000 persons, with approximately 3,000 new cases in the Netherlands[1, 2] and 65,000 new cases in the US[3] annually. The number of NHL survivors has increased rapidly from 13,400 in 2001 to 19,600 in 2008 in the Netherlands[1, 2] and from approximately 347,000 in 2001 to 454,000 in 2008 in the US[3]. An individual has a 1 in 50 chance of being diagnosed with NHL during his or her lifetime.

As cancer survivors live longer, they develop risks such as late effects of therapy and adverse physical and psychosocial long-term effects[4]. These long-term effects include persistent fatigue, depression, anxiety and marital disruption that can have a negative influence on survivors' health-related quality of life (HRQoL)[5-10]. While cancer survivors may be expected to return to normal life soon after treatment ends, they may continue to be burdened by the physical and psychosocial effects of the cancer and related treatments.

In a recent systematic review, we found that, on average, lymphoma cancer survivors have decreased HRQoL compared to the general population even several years post-diagnosis (i.e., no resolution at more than five years post-diagnosis)[11]. However, most survivorship studies lack the use of an instrument that addresses the unique concerns related to the cancer experience such as those measured by the impact of cancer (IOC) scale[12-14]. This self-reported questionnaire was developed in the US to measure positive and negative impacts of cancer that long-term survivors attribute to their cancer experience. A translation of the IOC into Dutch has been undertaken, but its psychometric properties have not been described.

Cultural differences may affect the perception of the impact of cancer on HRQoL[15, 16]. Moreover, attitudes towards health practice and illness may also be defined by culture[17]. Therefore, we undertook an examination of two samples of NHL patients in the Netherlands and the US, and compared their responses to the IOC. To better understand the commonality of psychosocial problems between cultures, it is important to examine cross-national differences[18]. This undertaking will provide more knowledge of culture-specific determinants of psychosocial well-being. Therefore, the aims of the present study were to (1) perform an independent psychometric evaluation of the Dutch version of the IOCv2 in a NHL sample and (2) explore differences between Dutch and American NHL survivors regarding the impact of cancer and identify associations with socio-demographic and clinical characteristics associated with the IOC score.

METHODS

Participants

Dutch sample

NHL survivors aged ≥18 were identified using the Eindhoven Cancer Registry (ECR) to select all patients who were diagnosed with NHL between January 1st, 1999 and July 1st, 2009. We included all patients with indolent (including Chronic Lymphocytic Leukemia) and aggressive B-cell NHL as defined by the International Classification of Diseases for Oncology-3 codes (ICD-O-3)[19]. To identify and exclude patients who were deceased, the database was linked with the database of the Central Bureau for Genealogy, which collects data on all deceased Dutch citizens through the civil municipal registries.

Data collection took place in summer 2009 and was done within PROFILES (Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship). PROFILES is a registry for the study of the physical and psychosocial impact of cancer and its treatment from a dynamic, growing population-based cohort of both short and long-term cancer survivors. PROFILES contains a large web-based component and is linked directly to clinical data from ECR. Details of the data collection method have been previously described[20].

Of the 1,026 eligible survivors who were assumed to have received an invitation, 824 (80%) returned survey materials. Non-respondents were more often diagnosed with indolent NHL (63% versus 54%, p<0.05) and less often diagnosed with stage I disease (19% versus 25%, p<.05). There were no differences between respondents and non-respondents in gender or age.

American sample

NHL survivors were identified through Duke University Medical Center and University of North Carolina at Chapel (UNC) Hill Lineberger tumor registries in November 2004 as previously described[21]. Patients were eligible if ≥18 years old at diagnosis, and ≥2 years post-diagnosis. Prospective participants were mailed a self-administered survey. Of the 1,195 eligible survivors who were assumed to have received an invitation, 886 (74%) returned survey materials. Participants, compared with non-participants, were less frequently African American (10% versus 20%, p<0.001) and older at study enrolment (mean age 62.9 versus 58.8 years p<0.001).

Total sample

To create more comparable samples, we selected those survivors with overlapping ICD-O-3 codes, i.e. excluding survivors diagnosed with Chronic Lymphocytic Leukemia in the Dutch sample and survivors with T-cell and NK-cell NHL in the American sample. We also excluded survivors diagnosed ≤2 years post-diagnosis in the Dutch sample since the IOC was developed for longer term survivors and the US sample included only this population[13, 14]. The total sample consisted of 1229 survivors, 491 Dutch and 738 American survivors (Figure 1). Institutional Review Board approval was obtained in both countries at all institutions participating in the study and written informed consent was obtained from each participant.

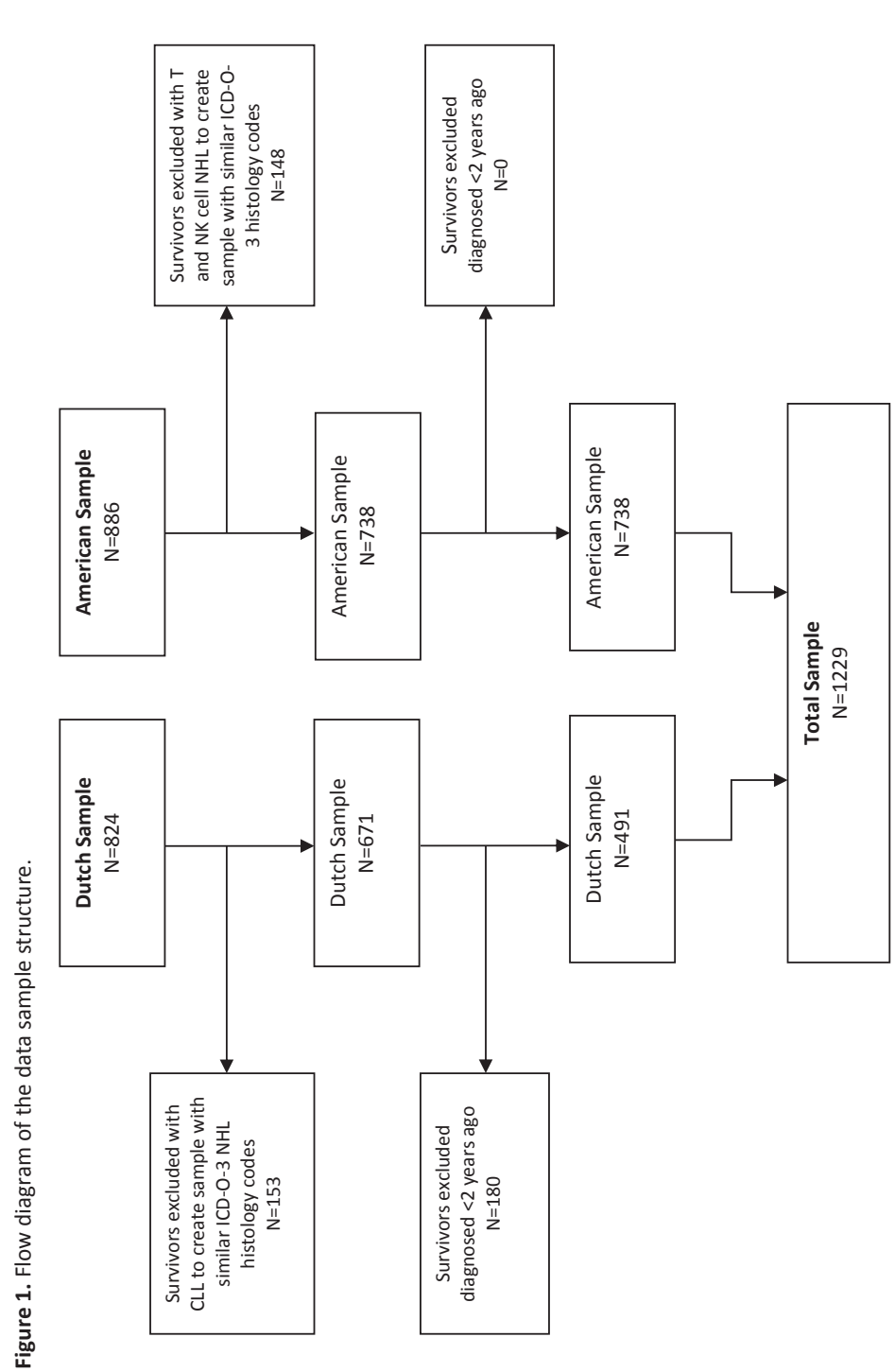

Figure 1. Flow diagram of the data sample structure.

Note. Flow diagram of the data sample structure, excluding patients with non-similar International Classification of Diseases for Oncology-3 (ICD-O-3) codes and those diagnosed less than two years post-diagnosis. CLL=Chronic Lymphocytic Leukemia, NHL=non-Hodgkin lymphoma, NK=natural killer.

Measures

The IOC presents statements regarding specific impacts of cancer to which respondents indicate their level of agreement from 1 (strongly disagree) to 5 (strongly agree). Initial psychometric scaling of a 81-item IOC questionnaire yielded the 41-item IOC version 1 (IOCv1) [13, 14]. A more recent and comprehensive scaling of the IOC questionnaire yielded the 37-item IOC version 2 (IOCv2)[12]. The Dutch survivors completed the IOCv1, which is missing 7 items that are in IOCv2. A newly developed algorithm was used to impute the 7 missing IOCv2 item scores for the Dutch survivors based on their IOCv1 responses[22]. The American survivors completed the 81-item IOC questionnaire and had their responses scored as IOCv2 scales. Other reports from the American sample have used both the IOCv1 and IOCv2 scoring formats[9, 10].

The Dutch survivors also completed the Dutch validated version of the European Organisation for Research and Treatment of Cancer Quality of life Questionnaire (EORTC QLQ-C30) which assesses HRQoL in cancer patients[23]. Response categories range from 1 to 4. After linear transformation, all scales and single item measures range in score from 0 to 100. A higher score on function scales and the global health and quality of life scale implies a better HRQoL, whereas for symptoms (scales and items) a higher score refers to more symptoms[23].

For both samples, comorbidity was assessed with the Self-administered Comorbidity Questionnaire (SCQ)[24]. Marital status and educational level were also assessed in both samples. For the Dutch sample, clinical information was available from the ECR that routinely collects data on tumor characteristics, including date of diagnosis, tumor grade, histology, Ann Arbor stage[25], primary treatment, and demographic characteristics, including gender and date of birth. Clinical data pertaining to the American sample were obtained from Duke University Medical Center and University of North Carolina at Chapel Hill Lineberger Tumor Registries and complemented with self-reported data.

Statistical analysis

All statistical analyses were performed using SAS (version 9.1 for Windows; SAS Institute Inc., Cary, NC). P values of <0.05 were considered statistically significant. Differences in socio-demographic and clinical characteristics between Dutch and American NHL respondents were assessed using chi-square and t-tests.

Psychometric evaluation

An exploratory factor analysis was conducted on the 37 items of the IOCv2 of the Dutch sample. Factors were extracted using principal components; the number of factors was selected using eigenvalue >1 and scree plots and promax rotation were performed. We repeated the factor analysis three times, with six, seven and eight factors, as the scree plot showed a stabilization point after six and eight factors. Internal consistency of the IOCv2 of the Dutch sample was measured using Cronbach's alpha. The Cronbach's alpha coefficient should reach 0.7 or above to be judged as good internal consistency and reliability[26]. Concurrent validity was evaluated by calculating Spearman correlation coefficients between IOCv2 scales and EORTC QLQ-C30 subscales. We hypothesized that the IOCv2 positive scales would be uncorrelated with the EORTC QLQ-C30, because they measure distinct constructs. We hypothesized that the IOCv2 negative scales would be substantially correlated with the EORTC QLQ-C30, because limitations in functioning and having cancer-related symptoms could have negative impacts on one's QOL.

Comparison of Dutch and American survivors

The mean IOCv2 scores of the Dutch NHL survivors were compared with the scores of the American NHL survivors using independent sample t-tests. Multivariate linear regression analysis was performed to investigate the independent association between socio-demographic and clinical variables and IOCv2 scales for the samples (Dutch and American) separately and for the total NHL sample. Since there were no large differences between countries in associations between IOCv2 scores and socio-demographic and clinical variables, only results of the total sample are presented.

RESULTS

Sample characteristics

Comparisons between Dutch and American NHL survivors showed significant differences on most socio-demographic and clinical characteristics (all $p<0.001$) except for age, marital/partner status and NHL histology (Table 1). Dutch respondents were more often male, had on average a lower educational level and were less likely to be employed during study enrollment. Mean interval since diagnosis was shorter among Dutch survivors, who also had a smaller range of interval (i.e., standard deviation). Dutch survivors also reported fewer comorbid conditions. Despite statistically significant differences in disease stage and treatment, both survivor groups were most often diagnosed with stage I disease followed by stage IV disease, and chemotherapy and radiotherapy were the most common treatments received. The mean age at the time of survey for both groups was 63 years and about 80% of survivors were married or in a committed relationship.

Psychometric evaluation

Exploratory factor analysis

The six factor structure yielded the most interpretable solution. 'Health Awareness and Worry' emerged as a single factor as did 'Body Change Concerns and Life Interferences'. The additional factors represented the four other domains of the IOCv2, i.e. Meaning of Cancer, Positive Self-Evaluation, Altruism/Empathy, and Appearance Concerns (Appendix 1). Item IOC29 loaded higher on Meaning of Cancer than on Health Awareness (0.57 vs. 0.35). The emerging of Body Change Concerns and Life Interferences as a single domain was also observed in the factor analysis of the American NHL sample[27]. Cronbach's alpha was 0.88 for the Positive and 0.94 for the Negative Impact scales, respectively, and ranged from 0.75 to 0.93 for the subscales.

Concurrent validity

The correlations between IOCv2 Positive scales and the EORTC QLQ-C30 were all below 0.30, supporting the distinctive content of the IOCv2 Positive scales from this HRQOL measure (Appendix 2). With respect to IOCv2 Negative scales we observed an overall pattern of moderate ($r \geq 0.30$) to substantial correlation ($r \geq 0.45$) with the EORTC QLQ-C30. The strongest correlation

Table 1. Socio-demographic and clinical characteristics of Dutch and American non-Hodgkin lymphoma survivors.

	Dutch respondents N=491	American respondents N=738	
	N (%)	N (%)	p-value
Gender			<0.001
Male	290 (59)	363 (49)	
Female	201 (41)	375 (51)	
Age at time of survey: mean (SD)	63.0 (12.5)	63.0 (13.3)	0.98
<50 years	71 (15)	111 (15)	
50-64 years	174 (35)	273 (38)	
65+ years	246 (50)	339 (47)	
Education[$]			<0.001
Low	111 (23)	81 (11)	
Medium	291 (61)	353 (49)	
High	74 (16)	284 (40)	
Marital/partner status			0.16
Married/committed	390 (81)	567 (78)	
Not married/committed	92 (19)	164 (22)	
Employment status			<0.001
Currently employed	116 (25)	287 (42)	
Not employed or retired	339 (75)	400 (58)	
Years since diagnosis: mean (SD)	5.3 (2.2)	10.2 (7.3)	<0.001
2-4 years	263 (54)	180 (24)	
5-7 years	153 (31)	223 (26)	
8-10 years	75 (15)	151 (17)	
>10 years	0	293 (32)	
NHL histology			0.89
Indolent	226 (46)	314 (43)	
Aggressive	265 (54)	374 (54)	
Unknown	0	50 (6)	
NHL stage at diagnosis			0.001
I	153 (31)	183 (28)	
II	93 (19)	149 (18)	
III	75 (15)	133 (17)	
IV	146 (30)	205 (24)	
Unknown[#]	24 (5)	68 (13)	
Primary treatment/ treatment			<0.001
Radiotherapy	148 (30)	363 (49)	
Chemotherapy	343 (70)	618 (84)	
Biologic	0	224 (30)	
Active surveillance[+]	78 (16)	0	
Transplant*	28 (6)	126 (17)	
Surgery	33 (7)	237 (33)	
Self-reported comorbidity			<0.001
No comorbid condition	136 (30)	75 (10)	
1 comorbid condition	138 (31)	135 (19)	
2 comorbid conditions	93 (21)	141 (19)	
>2 comorbid conditions	86 (19)	374 (52)	

Note. [$]Education levels included low= no/primary school; medium= lower general secondary education/vocational training; or high= pre-university education/ high vocational training/university; [#]Tumor stage could not be determined in some subtypes of indolent non-Hodgkin Lymphoma. [+]Patients are under active surveillance and receive no therapy; *Transplant= autologous stem cell or bone marrow transplantation.

was observed between IOCv2 Body Change Concerns and Fatigue of the EORTC QLQ-C30 (r=0.61).

Comparison of Dutch and American survivors

Significant differences were observed between Dutch and American NHL survivors on all IOCv2 scales (all p<0.01) except for Meaning of Cancer and Life Interferences (Table 2). Dutch survivors scored lower on the Positive Impact subscales (i.e., Altruism/Empathy, Health Awareness and Positive Self-Evaluation) and higher on the Negative Impact subscales (i.e., Appearance Concerns, Body Change Concerns and Worry). The difference on the Positive Impact Summary scale was larger compared to the Negative Impact Summary scale (0.4 vs. 0.2 points, both p<0.01).

Multivariate linear regression analysis also showed lower Positive IOCv2 scores and higher Negative IOCv2 scores (p<0.001) for Dutch survivors (Table 3). Based on the total sample of Dutch and American NHL survivors, females scored significantly higher on several Positive Impact subscales and on Appearance Concerns. Older survivors scored significantly lower on both Positive and Negative Impact Summary scales. In addition, higher educated survivors showed less Altruism/Empathy, survivors without a partner reported more Worry, and survivors who were not employed or were retired showed less Life Interferences.

With respect to the clinical characteristics, survivors with a longer survival time post-diagnosis showed higher Positive Self-Evaluation scores, and less Negative Impacts on Body Change Concerns, and Worry. Survivors with an aggressive NHL histology reported less Worry. Furthermore, survivors with more advanced disease stage, especially stage IV disease, showed higher scores on Health Awareness and on all Negative Impact scales. Survivors treated with chemotherapy reported a higher Positive Self-Evaluation and Positive Impact Summary scale as well as higher scores on Body Change Concerns. Lastly, survivors with three or more comorbidities had higher Negative Impact subscale scores.

Table 2. Comparison of mean scores of the IOCv2 sub and total scales between Dutch and American non-Hodgkin's lymphoma survivors.

	Dutch Respondents N=491			American Respondents N=738					
IOCv2 Scale	Mean	SD	Range	Mean	SD	Range	Δ	p-value	Effect size r
Altruism/Empathy	3.3	0.8	1-5	3.9	0.9	1-5	-0.6	<0.001	0.33
Health Awareness	3.2	0.9	1-5	3.7	0.9	1-5	-0.5	<0.001	0.27
Meaning of Cancer	2.7	0.9	1-5	2.7	1.1	1-5	0	0.12	0
Positive Self-Evaluation	3.4	0.8	1-5	3.9	1.0	1-5	-0.5	<0.001	0.27
Appearance Concerns	1.8	0.9	1-5	1.7	0.9	1-5	0.1	0.004	0.06
Body Change Concerns	2.6	1.0	1-5	2.4	1.2	1-5	0.2	0.002	0.09
Life interferences	2.0	0.7	1-5	2.0	0.7	1-4.8	0	0.62	0
Worry	2.8	1.0	1-5	2.6	1.0	1-5	0.2	<0.001	0.10
Positive Impact Scale	3.1	0.6	1-4.9	3.5	0.8	1-5	-0.4	<0.001	0.27
Negative Impact Scale	2.4	0.8	1-4.9	2.2	0.7	1-4.8	0.2	0.001	0.13

Note. IOCv2= Impact of Cancer Scale version 2.

Table 3. Multivariate linear regression analyses of IOCv2 sub and total scales of Dutch and American non-Hodgkin lymphoma survivors (N=1229).

	Positive subscales			Negative subscales					
	Positive impact scale	Altruism/ Empathy	Health Awareness	Meaning of cancer	Positive self-Evaluation	Negative impact scale	Appearance Concerns	Body Changes	Life interferences	Worry
	Beta	Beta	Beta	Beta	Beta	Beta	Beta	Beta	Beta	Beta
Country										
USA	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
The Netherlands	-0.25**	-0.32**	-0.25**	-0.05	-0.23**	0.16**	0.18**	0.13**	0.08	0.13**
Gender										
Male	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Female	0.10**	0.09*	0.07	0.06	0.11**	0.03	0.14**	0.00	-0.01	0.02
Age	-0.13**	0.00	-0.16**	-0.17**	-0.09	-0.18**	-0.15**	-0.10*	-0.16**	-0.17**
Education										
Low	0.04	0.03	0.02	0.02	0.05	-0.02	0.00	-0.05	-0.03	-0.01
Medium	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
High	-0.08	-0.12**	-0.00	-0.07	-0.06	0.01	-0.01	-0.06	-0.03	0.06
Marital/partner status										
Partner	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
No partner	0.02	0.05	0.06	-0.04	0.01	0.06	0.02	0.05	0.01	0.08*
Employment status										
Currently employed	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Not employed/retired	0.01	0.03	-0.04	0.00	0.04	-0.09	-0.06	-0.06	-0.16**	-0.03
Years since diagnosis	0.04	0.01	-0.03	0.03	0.10*	-0.15**	-0.01	-0.19**	-0.06	-0.16**
NHL histology										
Indolent	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Aggressive	0.01	0.00	-0.01	0.02	0.01	-0.05	-0.02	-0.02	0.01	-0.09*
NHL stage										
I	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
II	0.09	0.09	0.07	0.07	0.05	0.09	0.05	0.05	0.06	0.10*
III	0.08	0.05	0.08	0.08	0.05	0.12*	0.08	0.10*	0.10	0.10*
IV	0.09	0.06	0.14**	0.03	0.05	0.16**	0.12*	0.13*	0.14**	0.15**
Chemotherapy										
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	0.09*	0.08	0.01	0.05	0.16**	0.05	0.02	0.13**	0.03	0.01
Radiotherapy										
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	0.04	-0.02	0.00	-0.09	0.01	-0.01	0.01	-0.00	-0.02	0.01
Comorbidity										
None	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
1	-0.03	0.03	0.05	-0.01	-0.02	0.09	0.07	0.10	0.08	0.07
2	-0.01	-0.04	0.03	0.01	-0.01	0.12*	0.11*	0.11*	0.09	0.09
3 or more	0.01	0.01	0.05	0.02	0.03	0.32**	0.23**	0.32**	0.31**	0.21**

Note. IOCv2= Impact of Cancer Scale version 2; * p<0.01; ** p<0.001

DISCUSSION

The findings of this study show that similar impact domains were observed for Dutch and American NHL survivors, providing evidence that the IOCv2 measures common and important survivor concerns across two different Western nations. The internal reliability and consistency of the Dutch scales were good and construct validity was observed between the IOCv2 negative scales and the EORTC QLQ-C30. Unfortunately, we could not evaluate the construct validity of the IOCv2 Positive Impact subscales, since the Dutch study did not have a relevant questionnaire that measured positive growth.

We also observed significant differences between Dutch and American NHL survivors, whereby Dutch survivors reported less positive impacts and more negative impacts of cancer. These differences, combined with construct validity, suggest that the IOCv2 scales are able to distinguish between cultures of the impacts of cancer, and this questionnaire is thus culturally sensitive. One explanation for these differences might be that living in different cultures cultivates other psychological resources which influence health. The structure of a society, such as the social safety net and health care systems, contributes to shaping population health and attitudes towards health care[28]. Individuals in the US are socialized to rely more on individual resources compared with collective resources in Western Europe[16, 29]. In the US, health care programs fall under the responsibility of the individual[30, 31], whereas in the Netherlands they are administered by the government[32, 33]. To be more responsible for one's own health care creates a situation wherein control must be exercised. This sense of control is reflected in the emergence of a patient autonomy movement that began in America during the 1970s. Since then, a shift was made from a more paternalistic relationship between physicians and patients to a more equal relationship[34, 35], whereby information provision is one of the key elements of patient autonomy[36]. Studies have shown that personal control is associated with better self-reported health[37, 38] since individuals who believe that they have some degree of control over their lives may be more likely to take action in difficult situations[39]. Furthermore, the sense of personal control is more prevalent in North America than in Europe[15], which might result in the ability to alter perceptions of the cancer experience in a more positive way among American survivors. Additionally, the hospitals where the American NHL survivors were treated have well-developed programs in cancer survivorship care. For example, support groups are readily available and Duke University Medical Center provides free psychosocial counseling and UNC social workers were available to assist patients free of charge. A recent study reported that social support is associated with more positive and less negative Impacts of cancer (Smith et al., under review). Therefore, the higher positive and lower negative impact scores of the American survivors might be ascribed partly to having received more social support. Other evaluation of the sample demonstrated that females scored significantly higher on the positive impacts of cancer (Smith et al., under review). However, in the Dutch sample no differences in impact between men and women were observed, which may reflect other differences between the genders across the two samples.

Our results related to the impact of cancer are largely consistent with another Dutch study of 562 melanoma survivors[40]. In both studies, it appeared that time since diagnosis, tumor stage, and comorbidity were found to be associated with negative impacts of cancer.

The present study had some limitations. Although the response rate was high for both samples and information was available on socio-demographic and clinical characteristics of the non-respondents in both samples, it remains unknown whether non-respondents declined to participate in the study because of poor health. In addition, the seven missing items for the IOCv2 were calculated with a newly developed algorithm which has not been tested in other samples yet. Furthermore, the US data were collected from two institutions only, which limits the heterogeneity of the American sample.

In spite of these limitations, this study provides important information about the valid use of the IOCv2 in the Netherlands and with a preliminary look at the cross-national difference of the IOCv2 between Dutch and American NHL survivors. Results suggest that Dutch NHL survivors have lower positive and higher negative impacts of cancer compared with their American counterparts. Higher positive impacts for US survivors might be explained by more personal control and availability of supportive services. Future research should focus on determinants of the impact of cancer in both Dutch and American survivors to gain better understanding of the factors that might improve it.

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Appendix 1. Exploratory factor analyses and reliability analyses of IOCv2 items for the Dutch non-Hodgkin lymphoma survivor sample (N=491).

		Dutch NHL survivors	
		Factor loadings	Cronbach's α
	Altruism/Empathy		.82
IOC64	Having had cancer has made me more willing to help others	0.84	
IOC63	Because I had cancer I am more understanding of what other people feel	0.66	
IOC62	I feel a special bond with people with cancer	0.60	
IOC65	I feel I should give something back to others	0.81	
	Health Awareness*		.75
IOC16	Having had cancer has made me more concerned about my health	0.81	
IOC15	I do not take my body for granted since I had cancer	0.73	
IOC17	I am more aware of physical problems or changes	0.65	
IOC29	Having had cancer made me take better care of myself	0.23***	
	Meaning of Cancer		.88
IOC55	Because of cancer I have more confidence in myself	0.85	
IOC56	Having had cancer has given me direction in life	0.80	
IOC54	Because of cancer I have become better about expressing what I want	0.81	
IOC58	Because of having had cancer I feel that I have more control of my life	0.90	
IOC53	Having had cancer turned into a reason to make changes in my life	0.63	
	Positive Self-Evaluation		.78
IOC32	I consider myself to be a cancer survivor	0.90	
IOC33	I feel a sense of pride or accomplishment from surviving cancer	0.85	
IOC37	I feel that I am a role model	0.53	
IOC34	I learned something about myself because of having had cancer	0.55	
	Appearance Concerns		.80
IOC26	I worry about how my body looks	0.68	
IOC27	I feel disfigured	0.80	
IOC28	I sometimes wear clothing to cover parts of my body	0.81	
	Body Change Concerns**		.79
IOC25	I am bothered that my cannot do what it could before	0.63	
IOC24	I am concerned that my energy has not returned	0.60	
IOC39	Having had cancer has me feel old	0.54	
	Life Interferences**		.90
IOC67	Having had cancer has made me feel alone	0.79	
IOC57	I feel like cancer runs my life	0.78	
IOC68	Having had cancer has made me feel like some people do not understand me	0.83	
IOC40	I feel guilty today for not having been available to my family	0.46	
IOC73	Ongoing symptoms interfere with my life	0.76	
IOC70	Uncertainty about my future affects my decisions to make plans	0.86	
IOC72	Having had cancer keeps me from doing activities I enjoy	0.86	
	Worry*		.93
IOC23	Having had cancer make me feel uncertain about my health	0.89	
IOC9	I worry about the future	0.75	
IOC8	Having had cancer makes me feel unsure about the future	0.78	
IOC21	I worry about cancer coming back or getting another cancer	0.79	
IOC22	New symptoms make me worry about cancer coming back	0.74	
IOC19	I worry about my health	0.76	
IOC12	I feel like time in my life is running out	0.47	
	Positive impact scale		.88
	Negative impact scale		.94

Note. IOCv2=Impact of Cancer Scale version 2, NHL= non-Hodgkin lymphoma *Body change concerns and life interferences emerged as a single domain. **Health awareness and worry emerged as a single domain. *** Item IOC29 loads higher (0.53) on Meaning of Cancer.

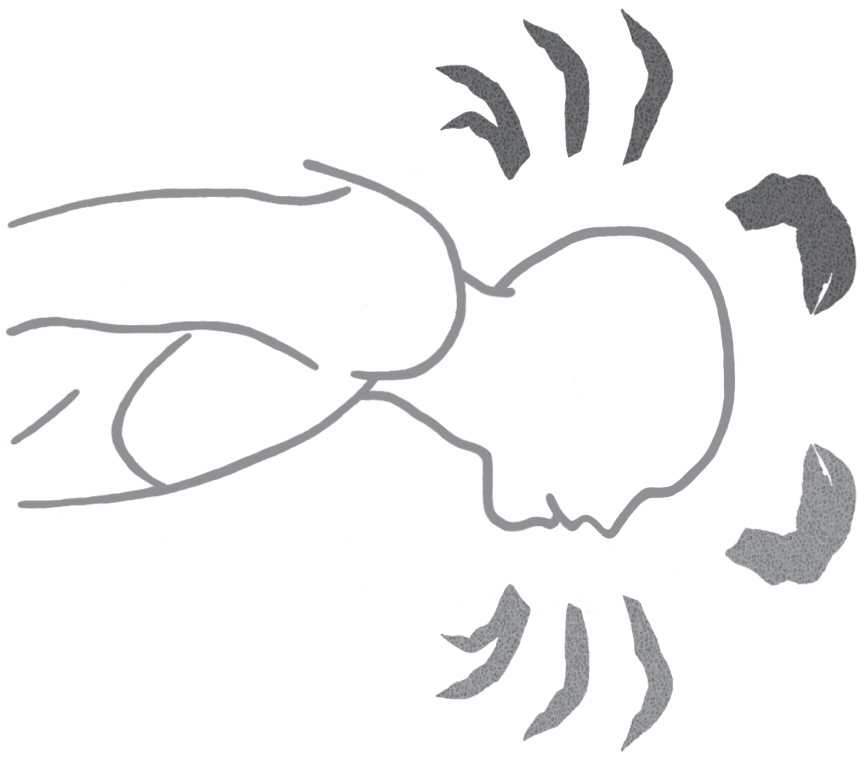
Appendix 2. Correlations (r) of EORTC QLQ-C30 with IOCv2 scores in the Dutch non-Hodgkins lymphoma survivor sample (N=491).

	Positive subscales					Negative subscales				
EORTC QLQ-C30	Positive impact scale	Altruism/ Empathy	Health Awareness	Meaning of cancer	Positive self-Evaluation	Negative impact scale	Appearance Concerns	Body Changes	Life interferences	Worry
Physical functioning	-0.10	-0.05	-0.16	-0.07	0.04	-0.54**	-0.42*	-0.59**	-0.56**	-0.33*
Role functioning	-0.09	-0.02	-0.18	-0.07	0.09	-0.49**	-0.36*	-0.55**	-0.51**	-0.32*
Emotional functioning	-0.12	-0.08	-0.28	-0.06	0.05	-0.54**	-0.29	-0.52**	-0.42*	-0.49**
Cognitive functioning	-0.11	-0.04	-0.17	-0.06	0.01	-0.35*	-0.28	-0.39*	-0.38*	-0.23
Social functioning	-0.14	-0.06	-0.26	-0.06	0.02	-0.51**	-0.30*	-0.54**	-0.50**	-0.37*
Quality of life	-0.08	-0.05	-0.24	-0.05	0.15	-0.56**	-0.36*	-0.57**	-0.55**	-0.40*
Fatigue	0.15	0.04	0.25	0.13	-0.04	0.54**	0.38*	0.61***	0.52**	0.38*
Nausea/vomiting	0.08	0.05	0.16	0.05	-0.06	0.31*	0.22	0.29	0.32*	0.22
Pain	0.09	0.05	0.15	0.08	-0.01	0.36*	0.24	0.38*	0.34*	0.26
Dyspnea	0.11	0.05	0.19	0.09	-0.02	0.43*	0.30*	0.45**	0.39*	0.31*
Sleep disturbances	0.05	0.01	0.17	-0.01	-0.05	0.33*	0.22	0.33*	0.31*	0.26
Appetite loss	0.08	0.05	0.13	0.05	-0.05	0.33*	0.26	0.33*	0.31*	0.22
Constipation	0.03	0.03	0.14	-0.01	-0.09	0.18	0.14	0.18	0.18	0.15
Diarrhea	0.01	-0.01	0.06	-0.00	-0.06	0.23	0.18	0.20	0.27	0.15
Financial Problems	0.14	0.11	0.16	0.11	0.07	0.33*	0.23	0.36*	0.29	0.25

Note. EORTC QLQ-C30= European Organization for Research and Treatment of Cancer Quality of Life Core questionnaire, IOCv2= Impact of Cancer Scale version 2.
*0.30≤ r <0.45; **0.45≤ r <0.60; ***r ≥0.60; and p<0.001 for test that correlation equals zero.

CHAPTER 10

Summary and general discussion



SUMMARY OF RESULTS

This thesis started with a systematic literature review focusing on health-related quality of life (HRQoL) of patients with Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) (**Chapter 2**). The aims were to identify the HRQoL domains that were most affected, study the impact of clinical (including treatment) and socio-demographic factors on HRQoL, and investigate the methodological strengths and limitations of the literature. Twenty-four articles were identified, 14 focusing on HL and 10 on NHL. The shortcomings of these studies were mainly the lack of a prospective design and the lack of information on non-respondents. The reviewed literature reflects that several domains of HRQoL, also in long-term lymphoma survivors, are affected. Compared to a normative population, HL survivors experience the most problems in (role) physical, social and cognitive functioning, general health, fatigue and financial problems, whereas NHL survivors experience the most problems in physical functioning, appetite loss, vitality and financial problems. In addition, HL survivors with older age and females reported worse outcomes. The results are less clear for NHL as only a few studies were performed. Furthermore, these studies were mainly focusing on all NHL subtypes combined instead of major subtypes of NHL.

As an answer to the limited attention for subtypes of NHL, we performed three studies on the impact of treatment on the HRQoL of patients with diffuse large B-cell lymphoma, (DLBCL), follicular lymphoma (FL) and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). The population-based Eindhoven Cancer Registry was used to select all patients diagnosed with DLBCL, FL and CLL/SLL from 2004-2010 and respectively 256 (84%), 148 (82%) and 136 (78%) patients responded.
Patients with DLBCL who were treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone every two weeks (R-)CHOP14 more often reported tingling in hands and feet, were more often fatigued and had more often a slowed down feeling compared to patients treated with (R-)CHOP every three weeks ((R-)CHOP21). Furthermore, older patients more often had persistent tingling in hands and feet and persistent worry about future health while a persistent slowed down feeling was reported more often by patients with comorbidities. Based on these observational findings with respect to HRQoL and symptoms, it seems that R-CHOP21 impacts less on HRQoL and symptoms of patients with DLBCL included in this study compared to R-CHOP14 (**Chapter 3**).

With respect to FL (N=148), HRQoL was worse among patients who underwent immunochemotherapy compared to an age- and sex-matched normative population. Patients under active surveillance or those who underwent radiotherapy reported similar HRQoL compared to the normative population, except for fatigue. Patients who received immunochemotherapy reported fatigue more often compared to patients who underwent radiotherapy. A quarter to 50% of patients reported persistent symptoms/worries over a one-year period such as worry about future health, feeling slowed down, lethargic, limited in social activities; they also exhibited significantly lower HRQoL than those without these symptoms/worries (**Chapter 4**).

CLL/SLL patients (N=136) whose malignancy was ever treated reported a significantly worse HRQoL than the normative population, whereas no differences were observed between the normative population and patients under active surveillance. Furthermore, younger patients tended to worry more about their future and patients with comorbid diseases reported more fatigue, more worry about their health and scored lower on physical functioning.
In contrast to our hypothesis, patients who received chlorambucil reported the worst HRQoL scores. We furthermore expected patients in the active surveillance group to worry most, since they were not actively treated for their cancer, but our data showed that patients who received chlorambucil worried significantly more. Long-lasting negative effects of starting treatment on HRQoL cannot be excluded, whereas active surveillance did not seem to provoke worrying, anxiety, or depressive symptoms in responders (**Chapter 5**).

As cancer patients with solid tumors often report anxiety, depressive symptoms and fatigue, we wanted to investigate the longitudinal prevalence of these symptoms among lymphoma patients. Anxiety and depressive symptoms were reported more often by responding patients with HL (N=180) and DLBCL (N=309) compared to the age- and sex-matched normative populations, i.e. patients reported rates between 17-24% and the normative populations between 11-14%. Over the four time points, approximately 10% of HL and DLBCL patients reported to be always anxious or depressed and an additional 15% sometimes. Importantly, global health status/HRQoL was lower in patients with anxiety or depressive symptoms and appeared to be constant over time (**Chapter 6**).

The level of persistent fatigue among NHL survivors was assessed in **Chapter 7**. The population-based Eindhoven Cancer Registry was used to select all patients diagnosed with NHL from 1999-2009; 824 survivors (80%) completed the first questionnaire and subsequently 434 survivors (53%) completed these questionnaires again one year later. The data showed that a majority of responders had a constant high level of fatigue up to 10 years after diagnosis. Six out of 10 survivors reported clinically relevant worse fatigue scores compared to the normative population. Also HRQoL was clinically relevant worse among survivors compared to the normative population. Fatigue mean scores remained significantly stable over a one-year period; 22-28% reported clinically relevant deterioration, whereas 19-23% reported clinically relevant improvement; 44-54% reported constant fatigue. Related to years since diagnosis, no clinically significant differences in mean fatigue scores were observed.

In **Chapter 8**, the level of perceived information, provision and satisfaction with this information among patients with lymphoma and multiple myeloma (MM, a plasma cell tumor) were investigated. Among 1,135 NHL, HL and MM survivors, 65% of indolent NHL, 67% of aggressive NHL, 74% of HL and 68% of MM survivors were satisfied with the amount of received information about their hematological malignancy and treatment trajectory. However, about one third of responding survivors were not satisfied and at least a quarter wanted more information. The topic that was mentioned most often when in need of more information was related to:
- late effects (37-50%),
- information on the cause and course of the disease (24-59%) and

- psychosocial aftercare (10-26%).

Young age, treatment with chemo, a recent diagnosis, using internet for information, and being without comorbidities were the most important determinants of higher perceived levels of information provision. The large variation in perceived information provision that was reported by patients from different hospitals, with an assumed similar patient population, suggest that there is room for improvement at hospital level.

To assess cultural differences between the HRQoL of American (from North Carolina; N=738) and Dutch (N=491) NHL survivors we performed a cross-national study comparing the positive and negative impact of cancer. We observed that compared to their American counterparts Dutch survivors scored:
- lower on the positive impact subscales (Altruism/Empathy, Health Awareness and Positive Self-Evaluation),
- higher on the negative impact subscales (Appearance Concerns, Body Change Concerns and Worry).

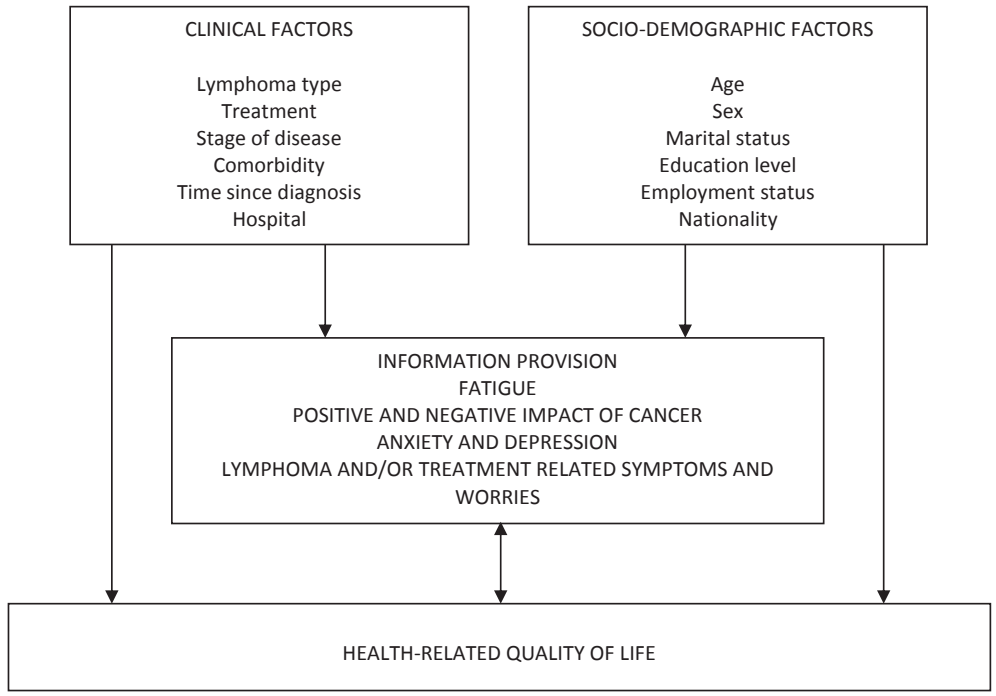
These findings seemed independent of socio-demographic and clinical characteristics (**Chapter 9**). Higher positive impacts for US survivors might be explained by more personal control and availability of supportive services in the investigated American hospitals.

GENERAL DISCUSSION

With the continuing improvements of new therapies among lymphoma patients, the rising incidence and the aging of the population, the number of lymphoma survivors will grow continuously. It is expected that in 2020 there will be 38,300 lymphoma survivors in the Netherlands[1] and 831,000 in the US[2], an increase of approximately 65% compared to 2010 in both countries. It is of utmost importance to evaluate the consequences of treatment on the health-related quality of life (HRQoL) of these patients, in order to optimize treatment and help clinicians to inform cancer patients about the potential (long-term) effects from the specific treatment they receive(d). The goal of new therapies should, besides improvement of survival, include achieving or maintaining optimal well-being. Not only after primary treatment but also long after treatment has ended, since many survivors are at risk for late effects of treatment[3-8].

The objective of this thesis was to gain knowledge and provide an overview of the associations between clinical factors such as treatment and lymphoma type and HRQoL. Besides, the relation between socio-demographic factors (such as age, educational level and nationality) and HRQoL and the relation between disease and/or treatment related symptoms and HRQoL was evaluated (Figure 1).

Figure 1. Conceptual model: associations between patient, tumor, treatment and hospital factors with patient reported outcomes.



LYMPHOMA TREATMENT IMPACTS ON THE HRQOL OF PATIENTS

DLBCL: RCHOP14 versus RCHOP21

In this thesis we observed that patients with diffuse large B-cell lymphoma (DLBCL) who received rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone every two weeks ((R-)CHOP14) reported more symptoms, among others neuropathy and a worse HRQoL compared to patients who received (R-)CHOP every three weeks ((R-)CHOP21). Short-term toxicity is known among these therapies[9, 10] as is neuropathy by more or less comparable treatment regimens[11, 12]. No studies had focused yet on the longer-term toxicity and self-reported HRQoL of lymphoma patients who underwent (R-)CHOP14 or (R-) CHOP21. An explanation for more neuropathy among patients treated with (R-)CHOP14 might be that these patients receive vincristine (with neuropathy as a known side-effect) in a quicker succession compared to patients treated with (R-)CHOP21. With respect to overall survival, it was thought that CHOP every 14 days was superior to a 21-day schedule[13], and therefore younger and fitter patients were more often treated with RCHOP14. However recently, two trials showed no differences in overall survival between RCHOP14 and RCHOP21 and advise RCHOP21 as the standard first line treatment for DLBCL[9, 10]. Based on these observational findings with respect to HRQoL and symptoms, it seems again that R-CHOP21 is the preferred treatment since it impacts less on HRQoL and symptoms of patients with DLBCL compared to R-CHOP14.

FL: immunochemo- and radiotherapy

We observed that patients with follicular lymphoma (FL) who underwent immunochemotherapy reported fatigue more often compared to patients who underwent radiotherapy. No other differences on the HRQoL or symptom scales were observed between these treatment types. Two other studies were identified that compared HRQoL between treatment regimes, although they evaluated other regimens compared to our study[14, 15]. Our observation of higher fatigue levels among patients who underwent immunochemotherapy can also result from the extensiveness of the disease, although there was no difference in HRQoL between patients who underwent one or more treatment lines. The discussion on how much treatment is optimal for FL is ongoing[16, 17]. In early stage FL it seems that patients benefit from radiotherapy with respect to overall survival but still many asymptomatic patients are not treated and are under active surveillance instead[18-21]. The number of early stage FL patients in our sample was too small to study differences in HRQoL between patients who underwent radiotherapy and patients under active surveillance. Future research, whereby we expand our HRQoL research to other regions of the Netherlands could evaluate this.

CLL: active surveillance versus chlorambucil versus intense immunochemotherapy

In contrast to our hypothesis, CLL/SLL patients who received chlorambucil and rituximab reported the worst HRQoL scores. Although their scores were not significantly different compared to CLL patients who underwent more intense immunochemotherapy, we expected a smaller impact of chlorambucil treatment, since chlorambucil is viewed as a 'simple' oral therapy. Our findings are not completely in line with a randomized clinical trial (RCT) that observed that HRQoL was better among patients treated with chlorambucil compared to patients receiving fludarabine. This difference was only observed during and not after treatment[22] and might furthermore be explained by the different settings in which the studies were performed, i.e. population-based study including elderly and frail patients versus an RCT with a strict selection of relatively healthy patients. We also expected patients in the active surveillance group to worry most, but patients who received chlorambucil worried significantly more. Due to the observational nature of our study we cannot exclude that patients with a lower HRQoL before treatment were more often treated with chlorambucil which may have influenced the results. Although, based on our observational findings it seems that starting treatment in CLL/SLL patients conveys a drastic, long-lasting negative effect on HRQoL, whereas active surveillance does not appear to provoke worrying, anxiety, or depressive symptoms. Our data therefore suggest that, with respect to HRQoL, it seems wise to stay conservative in starting treatment in asymptomatic patients.

Besides the impact of treatment, as discussed above, the disease itself could also affect the HRQoL of lymphoma patients. Therefore, it is important to notice that the deterioration in HRQoL can be a result of the disease itself, its treatment, or a combination of those.

The importance of including a normative population

To evaluate the specific impact of lymphoma and its treatment beyond the natural aging process and the impact of comorbidities, a comparison with an age- and sex-matched normative population was made. This comparison helps to define what 'normal' levels of functioning

are for people without cancer. In four articles of this thesis this comparison was made and worse scores for lymphoma survivors were observed. The HRQoL domains that were most affected were cognitive functioning (memory and concentration problems), social functioning (limitations in family life and social activities), fatigue, dyspnea and sleeping problems. Also financial problems were reported more often compared to the general population, which is a known problem among cancer patients[23]. Furthermore, higher rates for fatigue, anxiety and depressive symptoms compared with a normative population were observed in this thesis. These findings are consistent with the literature, that also shows worse HRQoL and higher prevalence of fatigue, anxiety and depressive symptoms among lymphoma patients compared to the general population[14, 24-38].

PATIENT AND CLINICAL CHARACTERISTICS ASSOCIATED WITH HEALTH-RELATED QUALITY OF LIFE: IDENTIFICATION OF PATIENTS AT HIGH-RISK

Besides treatment and lymphoma itself, socio-demographic and clinical factors may contribute to differences in HRQoL (Figure 1). This information was evaluated in order to identify patients at high risk for developing symptoms and deteriorated HRQoL.

Socio-demographic factors

Age and sex differences

In this thesis it was observed that among HL patients, younger women and older men reported higher levels of depressive symptoms. Female NHL patients reported more persistent fatigue. However, no consistent relation between gender and HRQoL can be drawn from the results in this thesis, which is in line with other studies among NHL patients that report contradicting results[33, 39, 40]. With respect to HL, there is some evidence that older patients and women report clinically important worse outcomes with respect to HRQoL[25, 30, 32, 41], although this was not observed in this thesis.

In this thesis it was observed that the difference in prevalence of anxiety and depressive symptoms was larger between HL patients and the normative population than the difference between DLBCL patients and the norm. This might suggest that since HL patients were on average 18 years younger, being diagnosed with lymphoma at an earlier age has a greater impact. In our study among 363 DLBCL patients we also observed larger differences compared to the norm for patients aged 18-59 than for patients aged 76-85 years[42]. An explanation might be that older patients may have better coping strategies through more life experience and they are likely to be faced with lower work-related and social demands and therefore experience less impact. So, on the one hand it seems logical to be careful with giving older patients toxic treatments since this could have a large impact on their HRQoL. However, it is also important to be careful with younger patients and not assume that they are able to take very aggressive therapies since they are young and relatively healthy. On the other hand, several studies show that older age in itself is stated by doctors as a reason for suboptimal treatment, even in the absence of a poor performance status[43-45]. It is often assumed that a standard treatment will lead to deterioration in HRQoL. The results of our study suggest that that is not the case in DLBCL survivors. However,

we cannot exclude that elderly patients perhaps received less aggressive treatment schedules. Either way, besides survival, treatment should also focus on achieving or maintaining optimal well-being to make sure that patients are able to live with the consequences.

Education

It was observed in this thesis that both HL and DLBCL patients who were lower educated experienced more anxiety and depressive symptoms compared to higher educated patients, which is consistent with previous research[31, 46]. It has been suggested that the adaptive needs such as problem solving and long-term planning are affected by the educational level of patients[47]. Furthermore, higher educated patients or patients with a higher socioeconomic status may be better able to understand and remember the information they have received and therefore better manage their disease. The understanding of the patients is an aspect that should receive more attention[48]. Awareness of the background characteristics of patients could help health care professionals to provide more patient-centered information.

Cultural differences

Differences between Dutch and American (from North Carolina) NHL survivors were observed in this thesis for the impact of cancer, whereby Dutch survivors reported less positive and more negative impacts of cancer. Could living in different cultures cultivate other psychological resources, which influence health? In the US, health care programs fall more under the responsibility of the individual[49, 50], whereas in the Netherlands they are the responsibility of the government[51, 52]. To be more responsible for one's own health care creates a situation wherein control must be exercised. Studies have shown that personal control is associated with better self-reported health[53, 54] since individuals who believe to have some degree of control over their lives may be more likely to take action in difficult situations[55]. Furthermore, the sense of personal control is more prevalent in North America than in Europe[56], which might result in the ability to alter perceptions of the cancer experience in a more positive way among American survivors. Since most cancer survivorship research is done in the US and it seems that there are differences between US and Dutch lymphoma survivors it is important to gain more knowledge about the experienced quality of care and quality of life reported by patients in the Netherlands.

Clinical factors

Comorbidity

In this thesis it was observed that compared to lymphoma patients (HL and/or NHL) without comorbidities those with concomitant diseases reported worse HRQoL, more fatigue, anxiety and depressive symptoms, more negative impacts of cancer and worried more about their future health. Research shows that comorbidity explains more variance in physical and emotional function, pain, and fatigue in comparison with socio-demographic and cancer characteristics in cancer survivors[57]. These findings emphasize the importance of alertness on comorbidity by health care professionals. Recognition of comorbidity will help to better tailor (after) care for patients with lymphoma or other cancers. When interpreting HRQoL results between groups, taking the presence of comorbid conditions into account, as was done in this thesis, is relevant as this influences the results. Studying comorbidity among lymphoma patients is also important as

many patients live long after their cancer diagnosis and are at risk for late effects of treatment[3-8]. Comorbidity should therefore be registered carefully and at several times since cancer diagnosis to distinguish between already existing comorbidity at time of cancer diagnosis and late effects of treatment. However, after diagnosis it becomes difficult to distinguish between (late) effects of treatment and comorbidity.

Time since diagnosis

No significant differences in HRQoL, fatigue, anxiety and depressive symptoms with respect to time since diagnosis were observed in all studies in this thesis. This is in line with a study among 761 NHL survivors[36]. A study among 459 HL patients even observed that patients 7-10 years after diagnosis reported higher anxiety and depression scores compared to patients 3-6 years after diagnosis[31]. So, while most lymphoma survivors may be expected to return to normal life soon after treatment ends, there is growing evidence that a large proportion continues to be burdened by the physical and psychosocial effects of the cancer and related treatment.

Tumor type

In this thesis it was observed that HL survivors reported a higher perceived level of and satisfaction with information than NHL and MM survivors. Patients' satisfaction is influenced by patients' expectations of the course of their disease[58] and these can vary widely, depending of the type of tumor. HL survivors may be more satisfied with and score better on perceived information since they have a better prognosis than NHL and MM survivors. Or maybe they actually receive more (and better) information since they are on average 20-30 years younger, and perhaps better educated, compared to the other patient groups.

CONTINUATION OF PROBLEMS AND ASSOCIATIONS BETWEEN SYMPTOMS AND HRQOL

In this thesis it was observed that at least a quarter of lymphoma survivors reported persistent disease and/or treatment related symptoms, 17-24% reported anxiety or depressive symptoms and 44-54% reported constant fatigue. Other researchers are also focusing on the persistence of symptoms and HRQoL among lymphoma patients[59]. It consistently seems that about 30% of lymphoma survivors report persistent problems. As described in the above sections, clinical and socio-demographic factors are associated with outcomes; however until now no specific profile for patients experiencing problems can be made. In this thesis no biological, psychological and environmental factors were included which might help to determine a potential profile.

This thesis furthermore shows negative associations, sometimes also longitudinal, between (persistent) disease and/or treatment related symptoms, anxiety and depressive symptoms and HRQoL. Alertness by patients and health care professionals for the presence of persistent symptoms that occur during and after treatment of lymphoma patients is needed and may help to avoid lasting negative influence on their HRQoL.

STRENGTHS, LIMITATIONS AND SUGGESTIONS TO IMPROVE POPULATION-BASED RESEARCH

Study design

A major strength of our studies is that HRQoL was assessed in a population-based setting, facilitated by the Eindhoven Cancer Registry (ECR) that includes patients with comorbidities and elderly patients. Studies focusing on populations including these patients are of critical importance as comorbidity and age affect the HRQoL of patients and influences treatment decision making[45, 60, 61]. Furthermore, the infrastructure of the PROFILES registry provides an excellent system for collecting HRQoL data of lymphoma patients and also for other tumors. The linkage between PROFILES and data from the ECR and PHAROS made it possible to evaluate the associations between clinical factors and patient-reported outcomes on a routine basis and to evaluate the impact of specific treatment regimens on the HRQoL of NHL patients.

Another strength is that, in the chapters 3, 4, 6 and 7 patients were examined at two or more time points. This longitudinal design provided insight into changes and the persistence of issues and is therefore important. However, the observational nature of our design limits in establishing causality and the results might be biased by confounding by indication, i.e. elderly and/or frail patients with a worse HRQoL are more likely to receive a less aggressive treatment compared to young and relative healthy patients. The inclusion of patients at different times since diagnosis (between 6 months and 10 years) moreover resulted in a heterogeneous group of patients with respect to survival time.

Comparative effectiveness research

To continue with the evaluation of the short- and long-term effects of the new and changing treatment regimens that are given to lymphoma patients, more comparative effectiveness research should be performed. Both RCTs and population-based observational studies have their advantages and disadvantages. In general, RCTs can be expensive and not always applicable to patients treated in daily practice while observational studies are somewhat limited in establishing internal validation since the absence of randomization. Recently, the suggestion of a randomized registry trial has been made, which might be a solution for the disadvantages of the study designs described above[62]. The idea of the randomized registry trial is to perform a trial based on a platform of an already-existing high-quality observational registry, in which detailed clinical data is embedded. Large patients groups can then be selected and randomized for a new trial. Although it sounds ideal, this design also has its limitations, it is for example not possible in every country and the question is if these data are complete enough and are of high enough quality. This should therefore be further explored. Until then it seems logical that the knowledge gained from clinical trials should be complemented by data from longitudinal population-based observational studies. Cancer registries are an excellent basis for this. The Netherlands Cancer Registry (NCR) collects data on primary treatment and in the Eindhoven Cancer Registry (ECR) also comorbidity at time of diagnosis is registered which is very valuable in the evaluation of quality of care. Although, in HRQoL assessment among (long-term) cancer survivors, the registration or collection of self-reported comorbidity data at time of questionnaire

completion is needed in order to evaluate the specific impact of patients current comorbid diseases on HRQoL.
Since patients are living longer and receive treatment when they have disease recurrence, follow-up registry of a specific number of items is required. PHAROS (an extension of the NCR) is the first registry in the Netherlands that started collecting follow-up data on among others treatment, adverse events and treatment outcomes, such as survival for hematological malignancies. To avoid getting lost in details and time consuming registration only a limited number of items should be registered.

In this thesis, data from PHAROS were used for several analyses. However, sample sizes for the evaluation of HRQoL were somewhat small since PHAROS, although started in 2009 was still in startup, but the registry is getting more and more complete. The impact of treatment on HRQoL of patients was investigated apart from survival. Future studies should focus on the combination of HRQoL and survival, to gather a more comprehensive perspective. Furthermore, since patients were included after treatment and baseline differences between treatment groups cannot be excluded as part of the explanation of the differences in HRQoL, future longitudinal population-based studies should also include HRQoL assessment before treatment. Moreover, to obtain a less heterogeneous patient group with respect to times since diagnosis, patients should be included at a fixed time since diagnosis and be followed from then on.

Response rates and representativeness of data
The number of patients responding to our questionnaire was high for the first measurement (75-85%). After that response rates began to decline, i.e. varying between 50-67% of the original cohort for the second measurement, around 40% for the third measurement and around 30% for the subsequent measurements. A meta-analysis reported average response rates for mailed cross-sectional surveys between 40-70%[63] so our response rate for the first measurement was much higher. The response rates for follow-up are similar to other longitudinal population-based observational studies. Since such studies are dependent of continuous cooperation of patients and referring, it always remains a challenge to maintain participation. To investigate ways to increase the response rate for patients who were invited for the third time, our research group conducted an experiment to evaluate the effectiveness of a monetary incentive on the response rate. Sixty lymphoma patients received a gift card of 10 Euros and the other 65 did not. It appeared that the gift card not only improved the overall response (90% versus 66%), it also quickened the response time. Furthermore, the cost of the incentive could outweigh the cost of having to send reminders.
Maybe even more important than the response rate is the representativeness of the data. We therefore always compared socio-demographic and clinical factors available from the ECR between respondents and non-respondents in our studies. Also the scores between patients who completed one, two or more questionnaires on outcomes of interest, such as HRQoL, were compared to verify potential selection bias. To even better understand the non-responder group and the group that stops participating after a certain measurement, future research could focus on the differences in disease and survival outcomes between these groups. It might be that non-respondents and patients who stop with the questionnaires are suffering more from their

lymphoma or even decease earlier. On the other hand it might be that they feel very well and do not feel the necessity to complete the questionnaires. Either way, for the representativeness of a study, future studies should collect as much data as possible on non-respondents, and explore why people stop participating, to identify possible bias.

Recruitment strategies
Hematologists and oncologists involved in the treatment and follow-up of lymphoma patients in the region of the ECR were asked to participate in our studies and almost all did (83%), indicating the interest and importance of the research. Since research assistants from PROFILES coordinated and facilitated the mailing of the questionnaires at each hospital, the effort requested of the specialists was little and this improved participation. This might not be possible in every country, but if so researchers should try to facilitate this as much as possible.

Determination of clinical relevance
When comparing scores of patients with those of normative populations or between treatment groups, it is important to use a certain criterion for clinical relevance of the results to identify the HRQoL domains and symptoms that are clinically relevant affected in patients. Although many studies base their conclusions on statistical significance, it is recommended to also use a criterion for the interpretation of clinical relevance to really attribute to the care of patients. For some questionnaires, such as the EORTC QLQ-C30, evidence-based guidelines have been developed for the determination of clinical important differences between groups and within patients over time[64, 65]. The differences can be divided into four size classes:
- large (representing unequivocal clinical relevance),
- medium (clinically relevant, but to a lesser extent),
- small (subtle but, nevertheless, clinically relevant)
- and trivial (circumstances unlikely to have any clinical relevance or being without a difference).

If no specific guideline is available for a questionnaire, then for example Norman's 'rule of thumb' can be used, whereby a ± 0.5 SD difference indicates a threshold of discriminating change in HRQoL scores[66].

Development of lymphoma specific HRQoL questionnaires
To measure HRQoL the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)[67] was used. HRQoL is a multidimensional construct that covers patients' perceptions of his or her physical, emotional, social and cognitive functions and disease and/or treatment related symptoms and represents patients' subjective experience with cancer. The EORTC QLQ-C30 is a cancer specific HRQoL questionnaire, but consists of such questions that this questionnaire (on for example memory and concentration problems, hair loss, fatigue and pain) is also applicable to the general population, to enable comparisons[68]. In addition to a cancer specific questionnaire, HL, NHL and CLL/SLL specific questionnaires should be used to detect side-effects and symptoms particularly relevant to these patients and survivors. HL, NHL and CLL/SLL specific questionnaires will be able to do this with more sensitivity compared to cancer specific questionnaires. In the absence of a true HL or NHL

HRQoL questionnaire, the EORTC CLL-16 was used to assess disease and treatment-related specific symptoms and worries for all (HL, NHL and CLL) patient groups. As the name suggests, this questionnaire was originally developed for patients with CLL/SLL. However, after discussion with specialists treating both CLL, HL and other NHL patients it was decided to administer the questionnaire for all lymphoma patients included in our studies.
Since a specific HL and NHL questionnaire is absent and the existing CLL/SLL module required an update, the EORTC Quality of life Group (QLG), with Lonneke van de Poll-Franse, Fabio Efficace and Simone Oerlemans as principal investigators, started with the development of a set of questionnaires to assess symptoms and HRQoL of these patients. Participants come from the UK, Italy, France, Austria, Taiwan and the Netherlands. The development consists of four phases, according to the guidelines of the EORTC QLG[69]. At the moment, phase I and II are completed and data collection for phase III is on-going. Phase I was aimed at compiling an exhaustive list of relevant HRQoL issues for CLL/SLL, NHL and HL patients, wherefore I performed extensive literature searches and held focus groups. Phase II consisted of the operationalization of the final phase I list of HRQoL issues into questions compatible with the EORTC QLQ-C30 in terms of format (response categories: 'not at all', 'a little', 'quite a bit', and 'very much') and time frame (one week). In phase III, the principal investigators as well as the collaborators from the UK, Italy, France, Austria, Taiwan and the Netherlands are now administering the questionnaire to the different patient groups to identify and solve potential problems in its administration and to identify missing or redundant issues. The aim is to complete phase III in 2014 and start with international field testing (phase IV) of the modules in 2015, so this questionnaire can soon be used in future research to assess disease and treatment specific concerns among these patients.

Future directions: improving HRQoL and care by interventions

The substantial rise in patients who have or ever had lymphoma will result in an increasing health care burden in hematology. To improve care for this growing group of cancer survivors, several initiatives are being undertaken and these as well as directions for the future will be discussed in this section.

Patient-centered information provision
An important aspect of patient care is the provision of information[70]. The goal of providing information is to prepare patients for their treatment, to increase treatment adherence and abilities to cope with cancer and to promote recovery[71]. Patients, who are well-informed about their cancer, treatment, and aftercare, are more likely to complete their therapy and are less anxious thereafter[72, 73]. Providing information is a difficult task since information is often complex, meant to make serious decisions, and potentially upsetting [74]. Information needs furthermore vary by sex, age, cultural background, time since diagnosis, educational level, stage of the disease and adjustment style[74, 75]. It can in this way reduce the psychological burden and improve patients' quality of life and their satisfaction with care[76, 77].
Personalized survivorship care plans could be a way to improve information provision and thereby care among lymphoma survivors. These personalized care plans consist of
- detailed information provision about diagnosis and treatment of cancer,

- possible long-term and late effects and management thereof,
- lifestyle and cancer surveillance recommendations, and
- available resources[78].

A recent trial among 43 oncology providers in the south of the Netherlands showed that oncology providers are generally positive about personalized care plans and are motivated to keep using it, they furthermore believe that patients are positively affected by it[79]. Another initiative with respect to improving information provision taken by the NFK (Dutch federation of cancer patient organizations), Dutch Cancer Society and Comprehensive Cancer Centre the Netherlands resulted in www.kanker.nl, developed in 2013. This website aims to provide patient-centered information, knowledge from cancer survivors and e-health focused on optimal quality of life. Through the library of www.kanker.nl visitors receive patient-tailored information, based on their profile. Leaflets of www.kanker.nl are available in most Dutch hospitals and health care professionals are encouraged to inform patient about the website.

Self-management
In the past decades, health care has changed through a gain in knowledge and technologies, whereby more and more patients take an active role in treatment decision and take responsibility for receiving good (after) care, also called self-management. Self-management is defined as 'the individual's ability to manage symptoms, treatment, physical and psychosocial consequences and life style changes resulting from their chronic illness'[80]. Also in the Netherlands, self-management is getting a more important role in cancer survivorship care[80]. Studies have shown that personal control is associated with better self-reported health[53, 54] since individuals who believe that they have some degree of control over their lives may be more likely to take action in difficult situations[55]. One of the key elements for personal control or self-management support is access to accurate and personalized information[81]. Self-management support is furthermore oriented at fostering intrinsic motivation and the acquisition of knowledge and skills. However, since patients vary in their existing knowledge and the amount and type of information they want or can understand as well as their expectations of the consultation, self-management support will not be profitable for everyone. It is therefore important that health care providers discuss patients' needs and expectations during consultations to be able to provide patient-centered care.

Intervening on self-management
Providing feedback and information to patients on their self-reported HRQoL and symptoms compared to results of other cancer patients or compared to a normative population might help empower patients to initiate to discuss the relevant topics with their physicians. I therefore performed a pilot study to investigate if patients would like to receive this kind of feedback. Of 47 lymphoma patients (response rate 73%), two-third reported that they would like to receive feedback on their reported HRQoL and symptoms and especially see their scores in comparison with other lymphoma patients (80%). To gain more evidence on how to support self-management in lymphoma cancer care, future studies should focus on interventions for supporting self-management[82]. For example by the provision of feedback and information on patients self-reported HRQoL and symptoms and by providing interventions to target specific information needs of patients.

Establishment of cancer survivorship clinics

To further improve care for lymphoma patients and survivors, a nationwide initiative of hematologists, radiation oncologists, epidemiologists and general internists has founded a working group named 'BETTER' ('BETER' in Dutch)[83]. 'BETTER' is currently developing protocols for standardized long-term care for HL and NHL survivors and establishing survivorship clinics. The goals of these clinics are to minimize the occurrence of late effects and to improve survivors' HRQoL by:

- informing survivors about long-term risks,
- advise preventive measures,
- suggest screening
- and improve aftercare by providing rehabilitation programs.

Inviting survivors for the 'BETTER' initiative could certainly be an efficient solution to improve care and address their lasting physical and psychosocial needs.

CONCLUDING REMARKS

Due to the ongoing improvements of new therapies, the rising incidence and the aging of the population, the number of lymphoma survivors will increase continuously. Both HL and NHL survivors experience physical and psychosocial problems as a result of cancer and its treatment, also long after completion of primary therapy. Furthermore, at least a quarter of lymphoma survivors reported persistent disease and/or treatment related symptoms, such as neuropathy and feeling lethargic, about half of patients worried about future health, 17-24% reported anxiety or depressive symptoms and 44-54% reported constant fatigue. Awareness and recognition of the specific health problems that lymphoma patients are facing is important to provide optimal supportive care. Strategies to improve this care, via the 'BETTER' initiative and the empowerment of patients, need to be examined.

Note. The data used for this thesis (data of patients and data of normative populations) are or become available at www.profilesregistry.nl and are free of use for non-commercial researchers.

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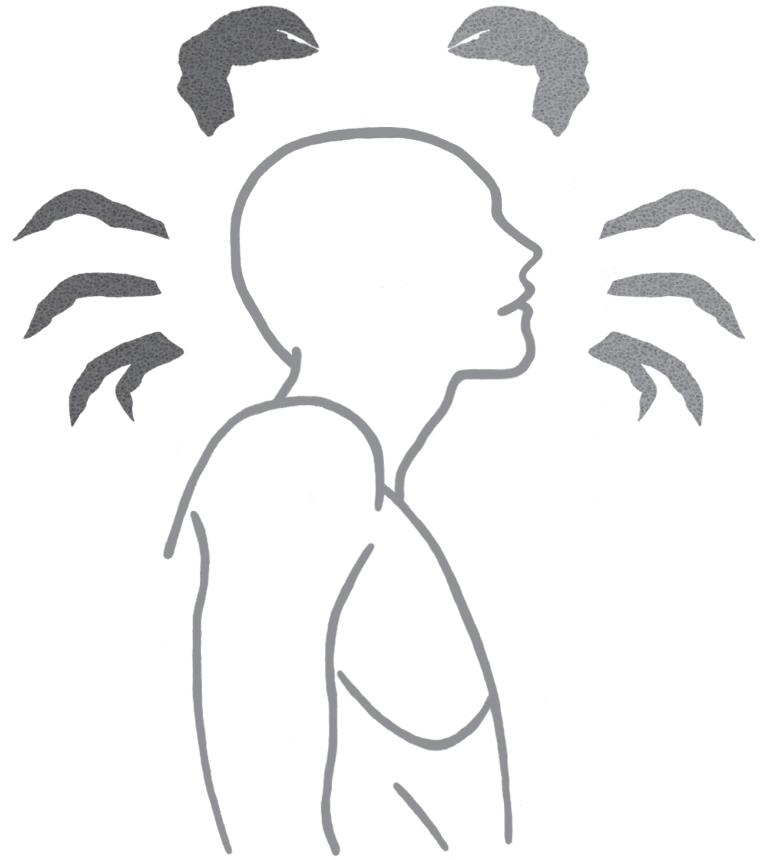
SAMENVATTING

(Summary)



INLEIDING

Lymfeklierkanker
Lymfeklierkanker is een vorm van kanker van het lymfestelsel en ontstaat doordat een afwijkende lymfekliercel abnormaal groeit. Lymfekliercellen, ook wel lymfocyten genoemd, zijn een soort witte bloedcellen. Er zijn twee grote groepen van lymfeklierkanker te onderscheiden, namelijk het Hodgkin lymfoom en het non-Hodgkin lymfoom. Het Hodgkin lymfoom is vernoemd naar Thomas Hodgkin, die in 1832 voor het eerst afwijkingen beschreef in het lymfestelsel. Het non-Hodgkin lymfoom is een verzamelnaam voor ongeveer vijftig verschillende soorten lymfeklierkankers die alle soorten omvat behalve het Hodgkin lymfoom. De meest voorkomende typen non-Hodgkin lymfoom zijn diffuus grootcellig B lymfoom, folliculair lymfoom en chronische lymfatische leukemie/klein lymfocytair lymfoom.

Behandeling van lymfeklierkanker
Gezien de grote variëteit aan soorten lymfeklierkanker is er niet één type behandeling. De behandeling voor lymfeklierkanker kan bestaan uit chemotherapie, bestraling, doelgerichte therapie, immunotherapie of stamceltransplantatie. Vaak wordt er een combinatie van deze behandelingen gegeven. Bij sommige soorten lymfeklierkanker hoeft er niet (meteen) behandeld te worden, omdat de lymfomen langzaam groeien of omdat de ziekte na behandeling meteen weer terug komt, dit beleid heet ‘wait and see’.

Toenemend aantal patiënten
Dankzij vroegere opsporing en verbeterde behandelingen leven patiënten met lymfeklierkanker steeds langer. Ook de vergrijzing van onze bevolking draagt bij aan de forse toename van het aantal (ex-)kankerpatiënten. In Nederland was de prevalentie (aantal mensen dat ooit de diagnose lymfeklierkanker kreeg en nu nog in leven is) in 1990 ongeveer 9.800 en verwacht wordt dat dit aantal zal stijgen naar ongeveer 38.300 in 2020.

Kwaliteit van leven
Doordat patiënten na de diagnose steeds langer in leven blijven, komt er meer aandacht voor de late en langdurige effecten van kanker en de behandeling op het welbevinden of de gezondheid gerelateerde kwaliteit van leven van (ex-)kankerpatiënten. Gezondheid gerelateerde kwaliteit van leven omvat het fysieke, emotionele, sociale en cognitief functioneren van een patiënt. Daarnaast omvat het de ziekte- of behandeling gerelateerde symptomen en vertegenwoordigt het de subjectieve ervaring van de patiënt met kanker. Studies tonen aan dat sommige (ex-) kankerpatiënten tot wel vijftien jaar na diagnose nog een verminderde kwaliteit van leven hebben in vergelijking met de algemene Nederlandse populatie. Daarnaast worden korte termijn effecten, zoals haaruitval, pijn en misselijkheid, lange termijn effecten zoals vermoeidheid, geheugen problemen en seksueel disfunctioneren en late effecten zoals tweede tumoren en hart- en vaatziekten geregeld gerapporteerd. De kennis op dit gebied is voornamelijk verzameld uit studies met patiënten met een veelvoorkomende kanker zoals borst-, dikke darm- of prostaatkanker.

Doel van dit proefschrift

Er is nog weinig bekend over de invloed van kanker en de behandeling op de kwaliteit van leven van patiënten die een vorm van lymfeklierkanker hebben of hebben gehad. Doordat steeds meer mensen lang na diagnose nog in leven zijn en er steeds nieuwe behandelingen worden ontwikkeld, is het belangrijk dat zowel de verbeteringen in overleving als de mogelijke bijwerkingen en invloed op kwaliteit van leven van deze nieuwe behandelingen worden geëvalueerd. Daarom heb ik in dit proefschrift gekeken naar wat de invloed van kanker en de bijbehorende behandeling is op zowel de korte als lange termijn gezondheid gerelateerde kwaliteit van leven van patiënten met verschillende soorten van lymfeklierkanker.
Het bestuderen van de korte en lange-termijn effecten van verschillende behandelingen geeft informatie over de medische en psychosociale behoeften van patiënten. Deze informatie draagt bij aan het evalueren van de functionele effectiviteit van de behandeling en helpt artsen en kankerpatiënten te informeren over de mogelijke late effecten van de specifieke behandeling die zij krijgen of hebben ontvangen.

Gebruikte databases

Om de onderzoeksvraag te beantwoorden ben ik een longitudinaal population-based onderzoek gestart bij patiënten met HL of NHL die geregistreerd werden in de Eindhovense kankerregistratie tussen 1999 en 2010. De gegevens met betrekking tot kwaliteit van leven en lange termijn effecten zijn verzameld in PROFILES en de gedetailleerde behandelingsgegevens werden verkregen via PHAROS. PROFILES is wetenschappelijk onderzoek naar kwaliteit van leven bij mensen die kanker hebben of hebben gehad en PHAROS is een uitbreiding van de kankerregistratie waarin extra gegevens over de behandeling van patiënten met lymfeklierkanker worden verzameld.
Gegevens over kwaliteit van leven werden ook verzameld van mensen zonder kanker uit de algemene Nederlandse bevolking om zo de gevolgen van kanker buiten het natuurlijke verouderingsproces en de invloed van bijkomende ziekten te bestuderen. Alle studies zijn uitgevoerd bij het Integraal kankercentrum Nederland (IKNL), locatie Eindhoven in samenwerking met Tilburg University en de tien ziekenhuizen in de regio.

BELANGRIJKSTE BEVINDINGEN VAN HET PROEFSCHRIFT

Literatuuroverzicht

In dit proefschrift ben ik begonnen met een literatuurstudie waarbij ik de literatuur met betrekking tot de gezondheid gerelateerde kwaliteit van leven (KvL) van patiënten met een Hodgkin lymfoom (HL) en non-Hodgkin lymfoom (NHL) heb bestudeerd (**Hoofdstuk 2**). Het doel was om te identificeren welke domeinen van kwaliteit van leven het meest zijn aangedaan in deze patiëntengroepen. Daarnaast werd de invloed van klinische (zoals behandeling en stadium van de ziekte) en sociaal demografische kenmerken op de kwaliteit van leven onderzocht. Tevens heb ik de methodologische sterke punten en beperkingen van de geïncludeerde studies bekeken. Vierentwintig artikelen die voldeden aan de vooraf gedefinieerde inclusiecriteria werden geïdentificeerd, veertien gericht op HL en tien op NHL. Deze werden beoordeeld op basis van een lijst met kwaliteitscriteria. De tekortkomingen van deze studies waren voornamelijk het ontbreken van een prospectieve opzet en het ontbreken van informatie over de non-

respondenten. Uit de literatuur kwam naar voren dat verschillende domeinen van kwaliteit van leven zijn aangedaan, zelfs nog jaren na diagnose. In vergelijking met een normatieve populatie, rapporteerden HL patiënten de meeste problemen in fysiek, sociaal en cognitief functioneren, algemene gezondheid, vermoeidheid en financiële problemen. NHL patiënten rapporteerden de meeste problemen in het fysieke functioneren, verlies van eetlust, vitaliteit en financiële problemen. Daarnaast rapporteerden HL patiënten die ouder waren en/of vrouw zijn meer beperkingen. Voor NHL waren de resultaten minder duidelijk, omdat er weinig studies werden uitgevoerd. Bovendien waren deze studies vooral gericht op alle NHL subtypes gecombineerd in plaats van op subtypes van NHL.

De invloed van kanker en bijbehorende behandeling

Uit het literatuuronderzoek bleek dat er nog nauwelijks onderzoek was gedaan naar subtypen van NHL. Daarom voerden we drie studies uit naar het effect van behandeling op de kwaliteit van leven van patiënten met de meest voorkomende subtypen van NHL, namelijk diffuus grootcellig B lymfoom (DLBCL), folliculair lymfoom (FL) en chronische lymfatische leukemie/klein lymfocytair lymfoom (CLL/SLL). De Eindhovense kankerregistratie werd gebruikt om alle patiënten met DLBCL, FL en CLL/SLL die in de periode 2004-2010 werden gediagnosticeerd te selecteren en respectievelijk 256 (84%), 148 (82%) en 136 (78%) van hen participeerden in het onderzoek.
Patiënten met DLBCL die elke twee weken de immuno-chemotherapie rituximab, cyclofosfamide, doxorubicine, vincristine en prednison (R-CHOP14) ontvingen, rapporteerden meer neuropathie (zoals tintelingen in handen en voeten) en meer vermoeidheid in vergelijking met patiënten die dezelfde immuno-chemotherapie elke drie weken ontvingen (R-CHOP21). Daarnaast rapporteerden patiënten behandeld met R-CHOP21 ook een betere algemene gezondheid en kwaliteit van leven dan patiënten behandeld met R-CHOP14. Tot voor kort werd gedacht dat behandeling met R-CHOP14 tot een betere totale overleving leidde dan R-CHOP21, maar recentelijk toonden twee studies geen verschil aan in totale overleving tussen beiden behandelingen. Daarom wordt R-CHOP21 nu als standaard eerstelijns behandeling gegeven. Op basis van onze bevindingen met betrekking tot kwaliteit van leven en symptomen is R-CHOP21 ook de voorkeursbehandeling (**Hoofdstuk 3**).

In **Hoofdstuk 4** observeerden we dat patiënten met FL (N=148) die immuno-chemotherapie ondergingen een slechtere gezondheid gerelateerde kwaliteit van leven rapporteerden in vergelijking met een normpopulatie van dezelfde leeftijd en geslacht. Patiënten die ‘wait and see’ volgden of radiotherapie ondergingen rapporteerden een vergelijkbare gezondheid gerelateerde kwaliteit van leven in vergelijking met de normpopulatie, met uitzondering van vermoeidheid. Daarnaast rapporteerden patiënten die immuno-chemotherapie ontvingen meer vermoeidheid ten opzichte van patiënten die radiotherapie ondergingen. Een kwart tot de helft van de patiënten met FL rapporteerden aanhoudende zorgen over hun toekomstige gezondheid, waren aanhoudend vermoeid en waren beperkt in het uitoefenen van sociale bezigheden.

Patiënten met CLL/SLL (N=136) die ooit werden behandeld voor hun kanker met chloorambucil of een andere (immuno-)chemotherapie ervoeren een slechtere kwaliteit van leven dan de algemene populatie, terwijl er geen verschillen werden waargenomen tussen CLL/SLL patiënten

die een ‘wait and see’ beleid volgden en de normpopulatie. In tegenstelling tot onze hypothese rapporteerden patiënten die chloorambucil kregen de slechtste kwaliteit van leven. Daarnaast verwachtten we dat patiënten die een ‘wait and see’ beleid volgden zich meer zorgen zouden maken over hun gezondheid, omdat ze niet ‘actief’ behandeld worden tegen hun kanker, maar de resultaten toonden aan dat patiënten die chloorambucil kregen zich aanzienlijk meer zorgen maakten (**Hoofdstuk 5**).

Prevalentie van vermoeidheid, angst en depressieve klachten

Uit onderzoek is gebleken dat kankerpatiënten met solide tumoren (zoals borst-, darm- of prostaatkanker) vaak angst, depressieve klachten en vermoeidheid rapporteren. Deze klachten komen hoogstwaarschijnlijk ook bij kankerpatiënten met niet-solide tumoren (zoals lymfeklierkanker) voor, alleen is het onbekend wat de prevalentie hiervan is en of deze klachten over de tijd blijven bestaan. Daarom hebben we de prevalentie van deze symptomen over een periode van vier jaar onderzocht bij een groep patiënten met lymfeklierkanker. Angst en depressieve klachten werden door 17-24% van de patiënten met HL (N=180) en DLBCL (N=309) gerapporteerd in vergelijking met 11-14% in de normpopulatie van dezelfde leeftijd en geslacht. Over de meetperiode van vier jaar, rapporteerden 10% van de HL en DLBCL patiënten altijd angstige of depressieve klachten te hebben. Daarnaast rapporteerden 15% soms angstige of depressieve klachten te hebben. Bij patiënten met deze klachten was de globale gezondheidstoestand en kwaliteit van leven aanzienlijk lager en deze relatie was constant over de meetperiode (**Hoofdstuk 6**).

In **Hoofdstuk 7** werd de prevalentie van aanhoudende vermoeidheid bestudeerd bij NHL patiënten; 824 patiënten (80%) vulden de eerste vragenlijst in en 434 (53%) patiënten vulden een jaar later nogmaals de vragenlijst in. De resultaten lieten zien dat de meerderheid van de patiënten aanhoudende vermoeidheid rapporteerde tot 10 jaar na de diagnose. Zes van de tien patiënten rapporteerden een klinische relevante hogere vermoeidheidscore dan de normpopulatie. Ook de gezondheid gerelateerde kwaliteit van leven was slechter onder patiënten in vergelijking met een normpopulatie. Over een periode van een jaar rapporteerde 22-28% een achteruitgang en 19-23% een verbetering in vermoeidheid. Aanhoudende vermoeidheid werd door 44-54% van de patiënten gerapporteerd.

De tevredenheid met informatievoorziening werd onderzocht in **Hoofdstuk 8** bij 1.135 patiënten met NHL, HL of multiple myeloom (MM, een plasmacel tumor). Vijfenzestig procent van de patiënten met indolent NHL, 67% van agressief NHL, 74% van HL en 68% van de patiënten met MM waren tevreden over de hoeveelheid ontvangen informatie m.b.t. hun hematologische maligniteit en zorgtraject. Echter, ongeveer een derde van de patiënten was niet tevreden en ten minste een kwart had behoefte aan meer informatie. De onderwerpen die het meeste werden genoemd door patiënten die behoefte hadden aan meer informatie hadden betrekking op: late effecten van de ziekte en behandeling (37-50%), het beloop en de oorzaak van de ziekte (24-59%) en psychosociale nazorg (10-26%). Jonge leeftijd, een behandeling met chemo, een recentere diagnose, het gebruik van internet voor informatie, en de afwezigheid van andere ziekten waren de belangrijkste determinanten van een hoger waargenomen niveau van informatievoorziening.

De variatie in waargenomen informatievoorziening en de aanzienlijke geobserveerde verschillen tussen ziekenhuizen suggereren dat er ruimte is voor verbetering.

In **Hoofdstuk 9** werden de positieve en negatieve gevolgen van kanker onderzocht en vergeleken tussen Nederlandse (N=491) en Amerikaanse (N=738, uit North-Carolina) NHL patiënten. In vergelijking met de Amerikaanse patiënten scoorden de patiënten uit Nederland:

- lager op de positieve gevolgen (altruïsme/empathie, gezondheidsbewustzijn, positieve zelf-evaluatie)
- hoger op de negatieve gevolgen (bezorgdheid over uiterlijk, bezorgdheid over veranderingen in het lichaam en bezorgdheid in het algemeen).

Deze bevindingen bleven ook bestaan na het in acht nemen van de verschillen in sociaal-demografische en klinische kenmerken tussen de twee onderzoeksgroepen. Cultuur lijkt invloed te hebben op de wijze waarop patiënten de gevolgen van kanker op het leven evalueren. De hogere scores op positieve invloeden van kanker die in de Amerikaanse groep werden waargenomen, worden misschien verklaard door de hogere mate van ‘verantwoordelijkheid voor jezelf’ die in Amerika geldt en/of de beschikbaarheid van goede nazorg in deze bepaalde Amerikaanse regio.

TOEKOMST: VERBETEREN VAN KWALITEIT VAN LEVEN EN ZORG DOOR INTERVENTIES

De aanzienlijke en continue stijging van de aantallen patiënten die lymfeklierkanker hebben of hebben gehad resulteert in toenemende gezondheidszorglasten in de oncologie. Om de zorg van deze groeiende groep kankerpatiënten die steeds nieuwe behandelingen ondergaan te verbeteren, is het herkennen en monitoren van specifieke klachten waar kankerpatiënten mee te maken krijgen zeer belangrijk. Met behulp van de kankerregistratie en PROFILES kunnen we dit ook in de toekomst blijven doen. Een ander belangrijk aspect is het aanbieden van informatie op maat. Uit onderzoek blijkt dat patiënten die goed geïnformeerd zijn over hun kanker, behandeling en nazorg meer kans hebben om hun behandeling te voltooien en minder angst ervaren. Het verstrekken van een persoonlijk nazorgplan voor iedere patiënt kan bijdragen aan betere informatievoorziening en daarbij de zorg voor lymfeklierkankerpatiënten mogelijk verbeteren. Deze persoonlijke nazorgplannen bestaan uit gedetailleerde informatie over de diagnose en behandeling van kanker, mogelijke lange-termijn en late effecten en de behandeling daarvan, aanbevelingen voor leefstijl en contactgegevens voor psychosociale hulp. Via de website www.kanker.nl kunnen patiënten na het aanmaken van een profiel ook informatie op maat krijgen. Deze website is een initiatief van de NFK (Nederlandse Federatie van kankerpatiëntenorganisaties) en is ontwikkeld in samenwerking met KWF en IKNL.

In de afgelopen decennia is de gezondheidszorg veranderd door een toename van kennis en technologie, waarbij steeds meer patiënten een actieve rol spelen in de behandelingskeuze en de verantwoordelijkheid nemen voor het ontvangen van goede (na)zorg, ook wel zelfmanagement genoemd. Het geven van feedback en informatie aan patiënten over hun zelf-gerapporteerde kwaliteit van leven en symptomen in vergelijking met resultaten van andere kankerpatiënten of vergeleken met een normatieve populatie zou kunnen bijdragen aan het verhogen van de

zelfmanagement van patiënten. Daarnaast kan het patiënten helpen om relevante onderwerpen te bespreken met de behandelend arts. Om te onderzoeken of patiënten daar behoefte aan hebben, voerde ik een pilotstudie uit. Van de 47 ondervraagde patiënten met lymfeklierkanker (respons 73%), gaf twee-derde aan dat ze graag feedback ontvangen op hun zelf gerapporteerde kwaliteit van leven en ziekte- en behandeling-gerelateerde symptomen. Vooral de mogelijkheid van het vergelijken van de eigen scores met de scores van andere patiënten met lymfeklierkanker werd als heel waardevol gezien: 80% van de patiënten zou dit graag willen. Om inzicht te krijgen over hoe zelfmanagement ondersteund kan worden in patiënten met lymfklierkanker zijn interventiestudies nodig.

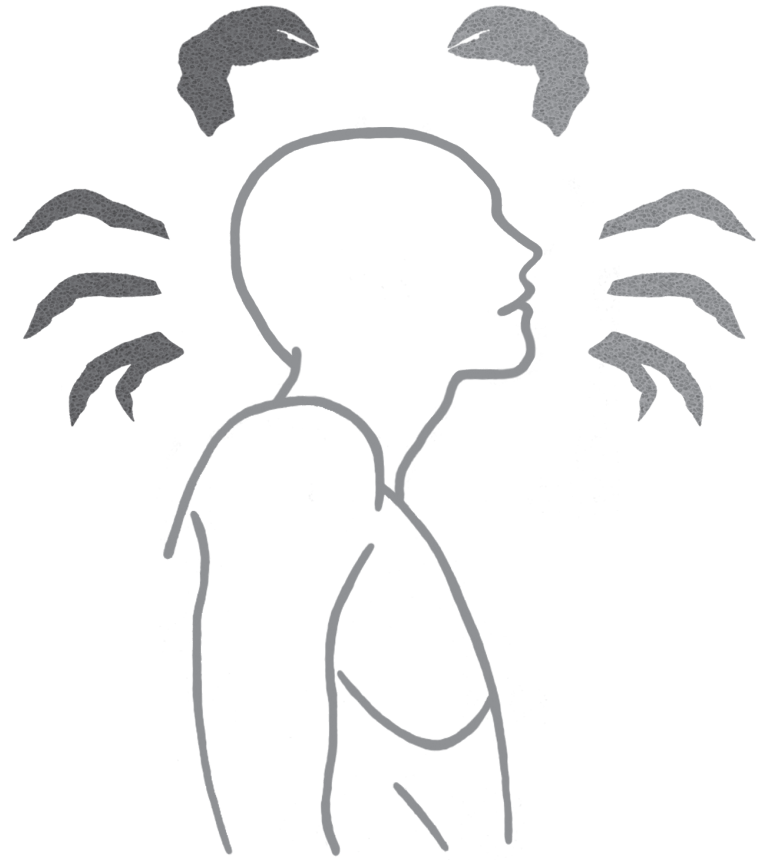
Om de zorg voor lymfeklierkankerpatiënten, in het bijzonder patiënten die meer dan vijf jaar geleden zijn gediagnosticeerd, verder te verbeteren is de nationale initiatiefgroep 'BETER' opgericht. Deze bestaat uit afgevaardigden van verschillende Nederlandse (academische) ziekenhuizen, waaronder hematologen, internisten, radiotherapeuten en epidemiologen. De groep heeft als doel de kwaliteit en de duur van de overleving bij patiënten met HL of NHL te verbeteren door ziekte en sterfte ten gevolge van late complicaties van de behandeling te verminderen. Door middel van het opzetten van poliklinieken in de academische ziekenhuizen zal er een gerichte zorg ontstaan voor overlevenden van HL of NHL, waardoor late effecten eerder worden herkend en beter worden behandeld. Andere doelstellingen zijn het informeren van patiënten over de lange termijn risico's, adviseren van preventieve maatregelen en screening en het verbeteren van nazorg door het verstrekken van revalidatieprogramma's. Het uitnodigingen van patiënten voor het 'BETER' initiatief kan een efficiënte oplossing zijn voor het verbeteren van de zorg en voor het aanpakken van blijvende lichamelijke en psychosociale behoeften.

CONCLUDERENDE OPMERKINGEN

Door de continue verbetering van behandelingen, de stijgende incidentie en de vergrijzing van de bevolking zal het aantal patiënten dat lymfeklierkanker heeft (gehad) sterk toenemen. Zowel patiënten met een Hodgkin als non-Hodgkin lymfoom ervaren fysieke en psychosociale problemen als gevolg van kanker en de behandeling, ook lang na voltooiing van de primaire behandeling. Bovendien wordt door ten minste een kwart van de lymfoompatiënten aanhoudende ziekte en/of behandeling gerelateerde symptomen gemeld, zoals neuropathie en een gevoel van lusteloosheid. Ongeveer de helft van de patiënten maakt zich zorgen over hun toekomstige gezondheid, 17-24% meldt angst of depressieve symptomen en 44-54% rapporteert aanhoudende vermoeidheid. Bewustwording en erkenning van de specifieke gezondheidsproblemen die lymfoompatiënten ervaren is belangrijk om optimale ondersteunende zorg te verlenen. Strategieën om deze zorg te verbeteren zoals het 'BETER' initiatief en het verhogen van zelfmanagement moeten worden onderzocht.

DANKWOORD

(Acknowledgements)



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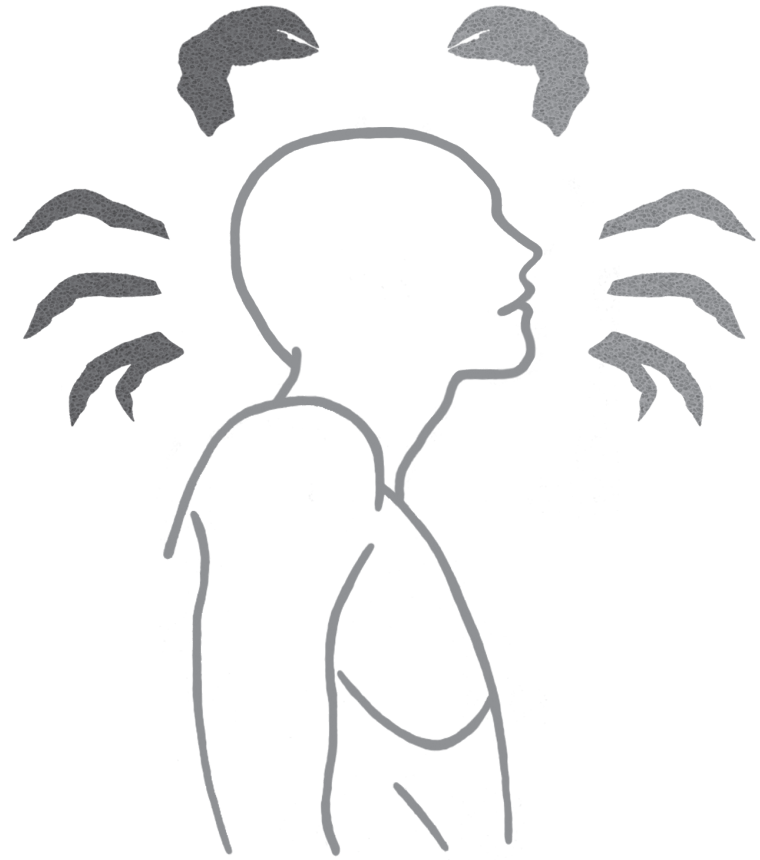
LIST OF PUBLICATIONS



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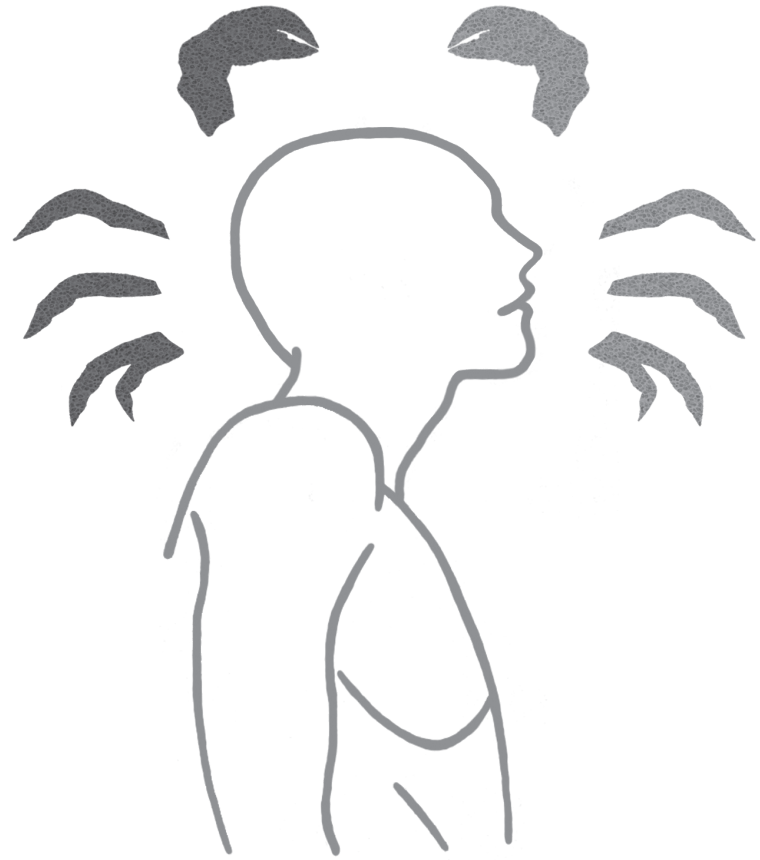

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Simone Oerlemans was born on October 23, 1983 in Eindhoven, the Netherlands. After she completed her pre-university education at Pleincollege Bisschop Bekkers in Eindhoven, she obtained her Bachelor's degree in Health Psychology at Tilburg University in 2006. Subsequently, she completed the Master program Health Psychology at the same institution in 2007. After working as a junior researcher at the Netherlands institute for health service research (NIVEL) in Utrecht, she started her PhD research at the Comprehensive Cancer Centre the Netherlands (IKNL), location Eindhoven and Tilburg University in 2009. Her research focused on the impact of cancer and its treatment on the health-related quality of life among lymphoma patients and survivors. Currently, she is working as a post-doctoral researcher at IKNL and developing an international validated quality of life instrument for lymphoma survivors within the Quality of life Group of the European Organisation for research and treatment of cancer (EORTC).